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Synthetically Useful Alkene Isomerisation and Hydroboration Reactions

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Synthetically Useful Alkene Isomerisation and Hydroboration Reactions

Paul Simon Fordred

A thesis submitted for the degree of

Doctor of Philosophy

University of Bath

Department of Chemistry

March 2012

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“The fool who persists in his folly will become wise.” –William Blake

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Last, but by no means least, for all of their unconditional support and assistance during recent years, I would like to thank my Mum and Dad, my brothers, Chris and Nick, and my wife, Silviya.

Abbreviations

Ac	Acetyl
Ad	Adamantyl
app.	Apparent
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
BARF	tetrakis(Perfluorophenyl)borate
BINAP	2,2'-bis(Diphenylphosphino)-1,1'-binaphthalene
BMS	Borane-dimethyl sulphide
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
BOM	Benzyloxymethyl
bp	Boiling point
Bu	Butyl
Bz	Benzoyl
c	Concentration
cat.	Catalyst <i>or</i> catalytic
Cbz	Carbobenzyloxy
COD	1,5-Cyclooctadienyl
COE	Cyclooctene
CM	Cross metathesis
Cp	Cyclopentadienyl
Cy	Cyclohexyl
δ	Chemical shift
Δ	Heat

d	Doublet <i>or</i> days
D	Dextrorotatory
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCE	1,2-Dichloroethane
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DMAP	4-Dimethylaminopyridine
DMB	Dimethoxybenzyl
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulphoxide
dppb	1,4-bis(Diphenylphosphino)butane
dppe	1,2-bis(Diphenylphosphino)ethane
dppp	1,3-bis(Diphenylphosphino)propane
<i>E</i>	Entegen (opposite, <i>trans</i>)
ee	Enantiomeric excess
ES	Electrospray
Et	Ethyl
Ether	Diethyl ether
equiv.	Equivalent
h	Hours
HMDS	bis(Trimethylsilyl)amide
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectrometry
IPA	Isopropanol

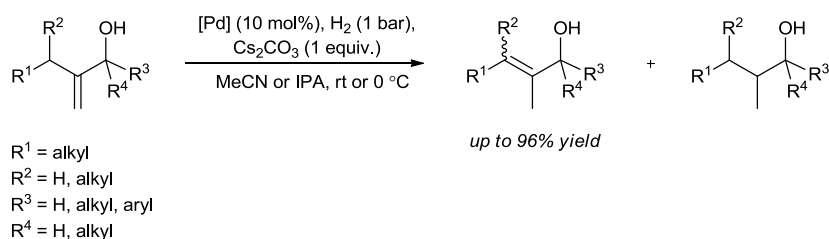
Ipc	Isopinocampheyl
<i>i</i> -Pr	Isopropyl
IR	Infrared
J	Coupling constant
L	Levorotatory <i>or</i> ligand
LDA	Lithium diisopropylamide
m	Multiplet <i>or</i> minutes
M	Metal
[M] ⁺	Molecular ion
mCPBA	<i>meta</i> -Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
MOM	Methoxymethyl
Ms	Methanesulphonyl
m/z	Mass charge ratio
NAP	2-Naphthylmethyl
nbd	Norbornadiene
NBS	<i>N</i> -Bromosuccinimide
<i>n</i> -Bu	<i>normal</i> -Butyl
NIS	<i>N</i> -Iodosuccinimide
NMR	Nuclear magnetic resonance
Np	Naphthyl
<i>n</i> -Pr	<i>normal</i> -Propyl
Ns	Nitrobenzenesulphonyl
<i>o</i>	Ortho
obs.	Obscured

<i>p</i>	Para
PCC	Pyridinium chlorochromate
Petrol	Petroleum ether (bp 40–60 °C)
Ph	Phenyl
Pin	Pinacolyl
Piv	Pivaloyl
PMB	<i>para</i> -Methoxybenzyl
PMP	<i>para</i> -Methoxyphenyl
PPTS	Pyridinium <i>para</i> -toluenesulphonate
Pr	Propyl
Py	Pyridyl
q	Quartet
RCM	Ring-closing metathesis
ROM	Ring-opening metathesis
RRM	Ring-rearrangement metathesis
rt	Room temperature
s	Singlet
SEM	2-(Trimethylsilyl)ethoxymethyl
Sia	Siamyl, 3-methylbutan-2-yl
t	Triplet
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -Butyl
TES	Triethylsilyl
Tf	Trifluoromethanesulphonyl
THF	Tetrahydrofuran

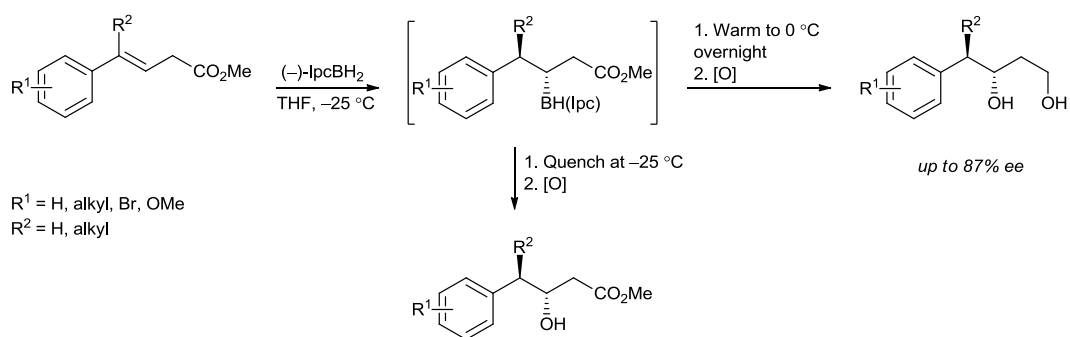
THP	Tetrahydropyranyl
Thx	Thexyl, 2,3-dimethylbutan-2-yl
TIPS	Tri- <i>iso</i> -propylsilyl
tlc	Thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethane-1,2-diamine
TMS	Trimethylsilyl
Tol	Tolyl
TPS	Triphenylsilyl
Tr	Trityl
Ts	<i>para</i> -Toluenesulphonyl
X _c	Chiral auxiliary
Z	Zusammen (together, <i>cis</i>)

Abstract

Upon treatment with a palladium catalyst and hydrogen gas in the presence of caesium carbonate, a wide range of exomethylenic allylic alcohols were found to afford their corresponding trisubstituted isomers. Although hydrogenation was an unavoidable competing pathway, careful monitoring of the reaction progress allowed the desired isomerised products to be obtained in moderate to excellent yields and high (*E*):(*Z*) ratios.



Asymmetric hydroboration reactions of a range of γ,δ -unsaturated methyl esters were found to afford their corresponding chiral 1,3-diols upon oxidation of the chiral organoborane intermediates, in a novel tandem reduction-hydroboration protocol. Alternatively, the chiral β -hydroxy ester product could be obtained by maintaining the reaction mixture at -25 °C.



1. Introduction

1.1 Synthetic applications of alkenes

Alkene bonds are a common structural feature of natural products and medicinally active compounds, as well as flavouring agents and perfume components.¹ Due to their stability and high reactivity, they can also function as reliable and versatile synthetic intermediates.² The enormous number of one-step transformations of alkenes which are known (Figure 1) facilitates rapid access to almost any functional group. As a consequence, numerous methods for the synthesis of alkenes have been devised.³ Many methods exist for their conversion into enantiopure compounds, with stereoselective variants of epoxidation,⁴ dihydroxylation⁵ and hydrogenation⁶ reactions all well established. In many cases, reversal of enantioselectivity can be readily achieved by using the opposite alkene geometric isomer, which is often significantly more convenient than preparation of a chiral catalyst/ligand in its antipodal form. A brief summary of the range of products that can be prepared using commonly employed alkene-functionalisation reactions is shown below in Figure 1.

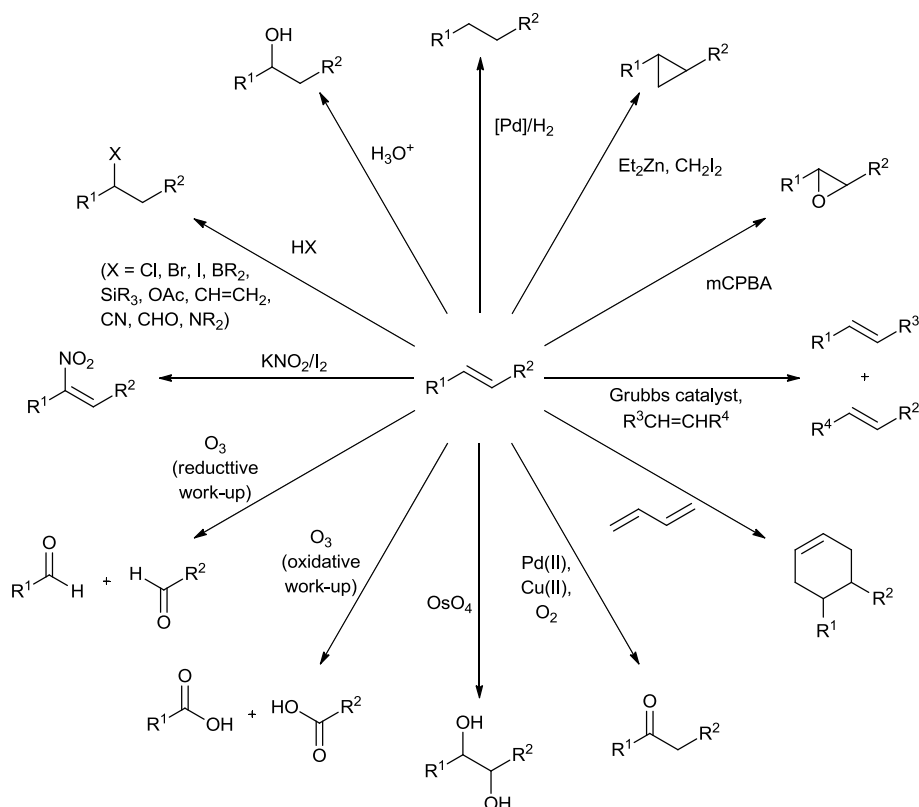
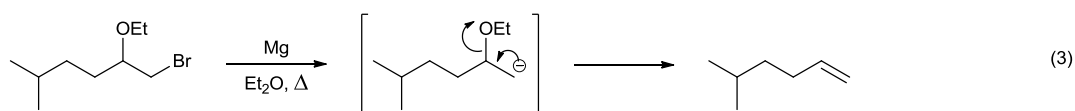
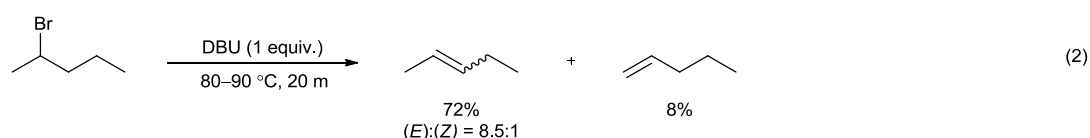
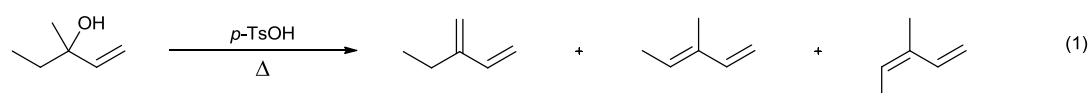


Figure 1. Selected one-step transformations of alkenes.

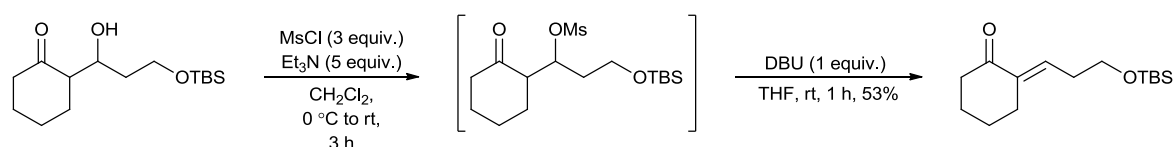
1.2 Protocols for the stereoselective synthesis of alkenes

The simplest alkene syntheses are based on elimination of HX (where X = halogen or O) from alkyl halides or alcohol derivatives *via* either E₁, E₂ or E_{1c}B elimination reactions (Scheme 1).^{7,8,9}



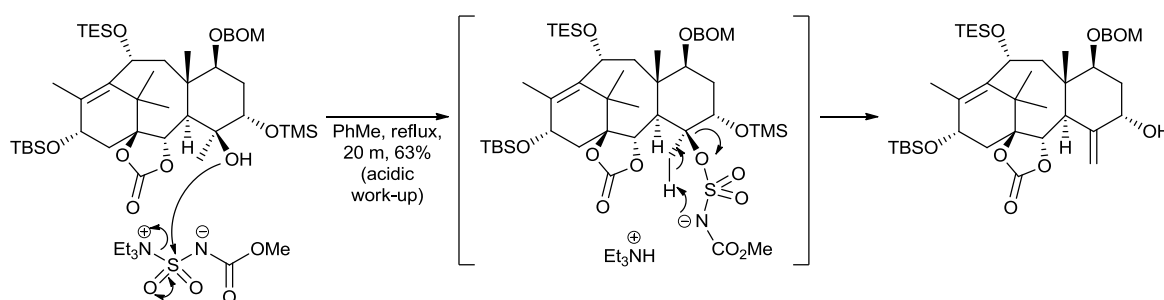
Scheme 1. Preparation of alkenes by E₁ (eq 1), E₂ (eq 2) and E_{1c}B (eq 3) elimination reactions.

Although these methods often utilise strongly acidic or basic conditions and can be poorly selective, they are simple and effective protocols for the preparation of simple alkenes, whilst the resulting product mixtures can potentially be purified by distillation. However, milder and more selective conditions are clearly desirable for the preparation of structurally complex alkenes that contain more sensitive functionality. An alternative method is to employ a two-step procedure involving initial conversion of an alcohol into a good leaving group, typically a tosylate or mesylate, followed by a base-induced elimination reaction (Scheme 2).¹⁰



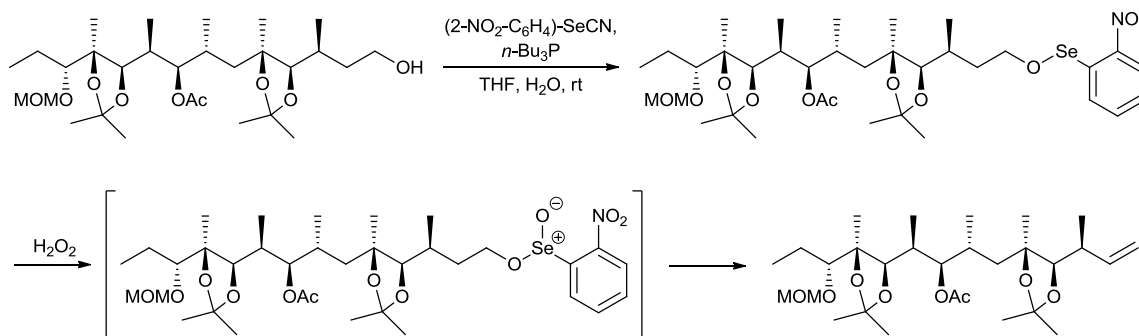
Scheme 2. Alkene synthesis *via* mesylate formation followed by base-induced E_{1c}B elimination.

A variety of other hydroxyl elimination methods which operate under relatively mild conditions have also been developed. For example, dehydration of secondary or tertiary alcohols can be carried out using the Burgess reagent – methyl *N*-(triethylammoniumsulphonyl)carbamate.¹¹ Initial attack of the alcohol functionality at the sulphur centre of the reagent occurs to displace its trialkylammonium fragment, followed by a rapid *syn*-elimination step that is initiated by β -deprotonation by the imide nitrogen. This type of elimination reaction was used during Holton's elegant total synthesis of taxol in 1994 (Scheme 3).¹²



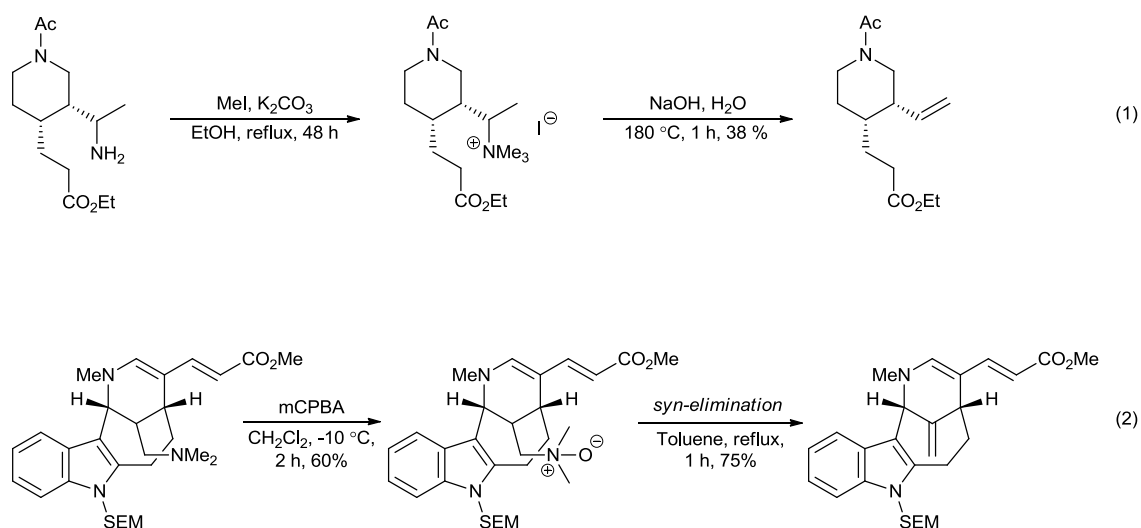
Scheme 3. Burgess dehydration reaction.

In 1976, Grieco¹³ reported a mild procedure for the dehydration of primary alcohols to form the corresponding terminal alkenes *via* elimination of a selenide intermediate. Reaction of the hydroxyl group with (2-nitrophenyl)selenocyanate in the presence of tributylphosphine results in formation of a selenide that is then oxidised with hydrogen peroxide to afford a selenoxide that is rapidly eliminated as a selenol intermediate (Scheme 4).¹⁴



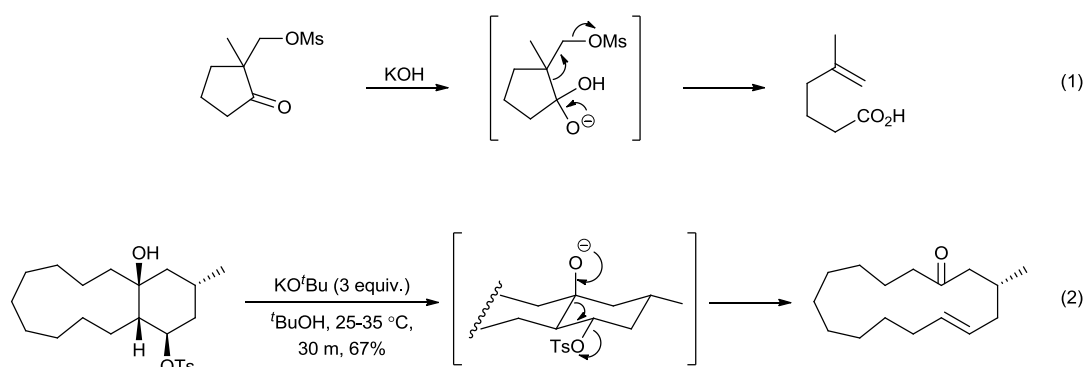
Scheme 4. The Grieco dehydration reaction.

Elimination reactions of amines have also been used for alkene synthesis, although they are less commonly encountered than their hydroxyl-based counterparts. The Hofmann elimination, first reported by Hofmann¹⁵ in 1851, consists of exhaustive methylation of an amino group with either methyl iodide or dimethyl sulphate, followed by base-induced elimination of the resultant quaternary ammonium salt under relatively harsh conditions (Scheme 5, eq 1).¹⁶ The Cope elimination reaction¹⁷ is a somewhat milder alternative, involving conversion of a tertiary amine into its corresponding *N*-oxide species, that is then eliminated by heating in an inert solvent (Scheme 5, eq 2).¹⁸



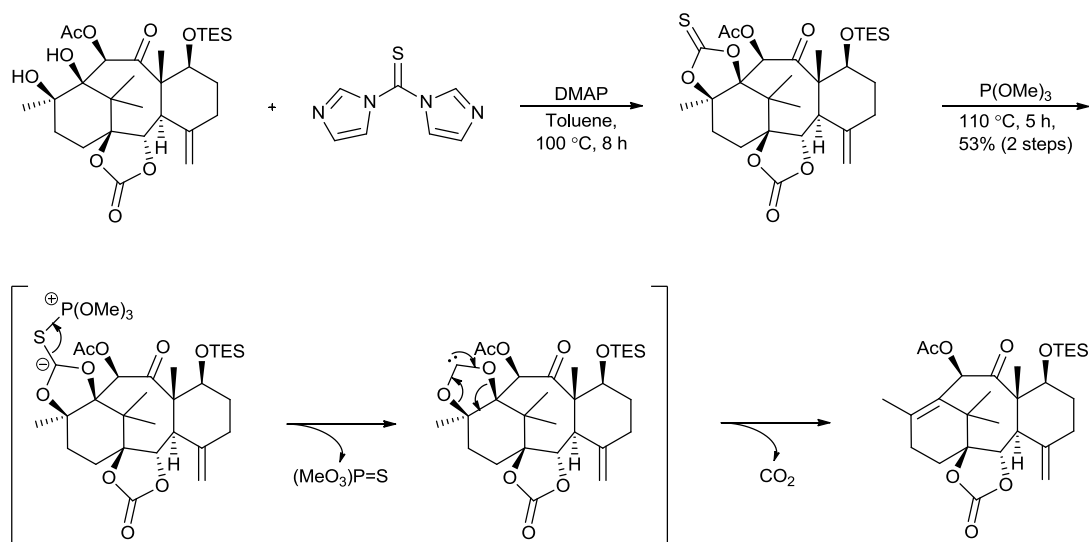
Scheme 5. The Hofmann elimination (eq 1) and Cope elimination (eq 2) reactions.

Alkenes can also be prepared *via* various fragmentation reactions, with the driving force of the reaction being provided by simultaneous formation of a carbonyl group.¹⁹ An early example was reported in 1952, by Eschenmoser,²⁰ who reported base-catalysed elimination reactions of various β -hydroxyketones to afford δ,ϵ -unsaturated carboxylic acids (Scheme 6, eq 1). Nowadays, these types of transformation are broadly classified as Grob²¹ fragmentations and represent an efficient means of selectively preparing cyclic alkenes that contain remote functionality (Scheme 6, eq 2).²²



Scheme 6. Alkene synthesis *via* base-induced fragmentation reactions.

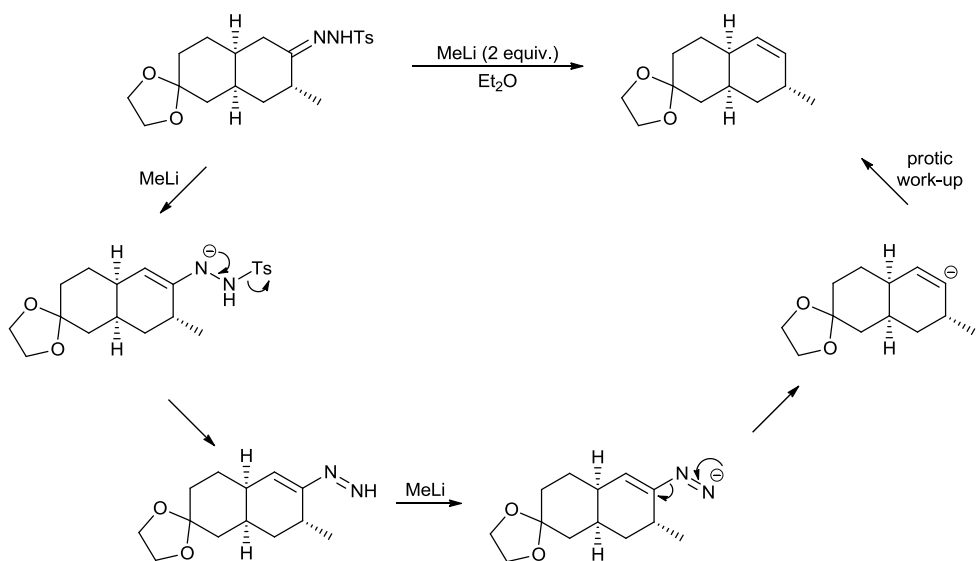
Alkenes can also be prepared from diols in a highly stereospecific manner, *via* the Corey-Winter²³ olefination protocol. First reported in 1963, this two-step procedure allows the stereospecific conversion of vicinal diols into their corresponding alkenes, *via* formation of an intermediate cyclic thionocarbonate, followed by phosphorus-mediated *syn*-elimination of sulphur and CO₂. An elegant example of this methodology was demonstrated in Mukaiyama's total synthesis of taxol in 1999 (Scheme 7).²⁴



Scheme 7. A Corey-Winter olefination reaction.

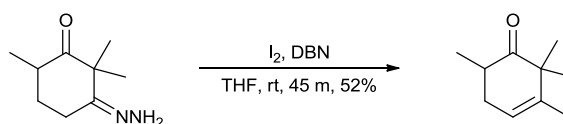
A potentially powerful strategy for alkene synthesis is the Shapiro reaction,²⁵ which consists of treatment of tosylhydrazone derivatives of ketones with two equivalents of a

strong base, which results in a regioselective elimination reaction for formation of the least-substituted alkene bond (Scheme 8).²⁶



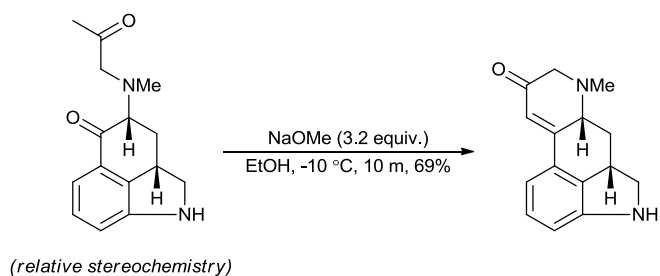
Scheme 8. The Shapiro reaction.

Alternatively, treatment of a hydrazone with iodine and DBN can afford a vinyl iodide product (Scheme 9),²⁷ which can then be further elaborated *via* metal-catalysed cross-coupling reactions as required.



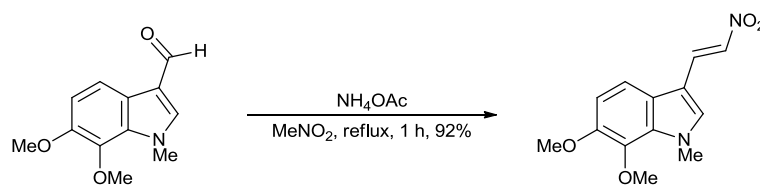
Scheme 9. The Barton vinyl iodide synthesis.

A number of well-established methods for alkene synthesis are based on condensation reactions involving carbonyl compounds. These protocols generally involve 1,2-addition of the enolate of a ketone to the carbonyl functionality of either an aldehyde or ketone acceptor, followed by elimination of water to afford an α,β -unsaturated carbonyl product. An intramolecular variant of this type of aldol condensation reaction was utilised by Woodward²⁸ during his total synthesis of lysergic acid (Scheme 10).



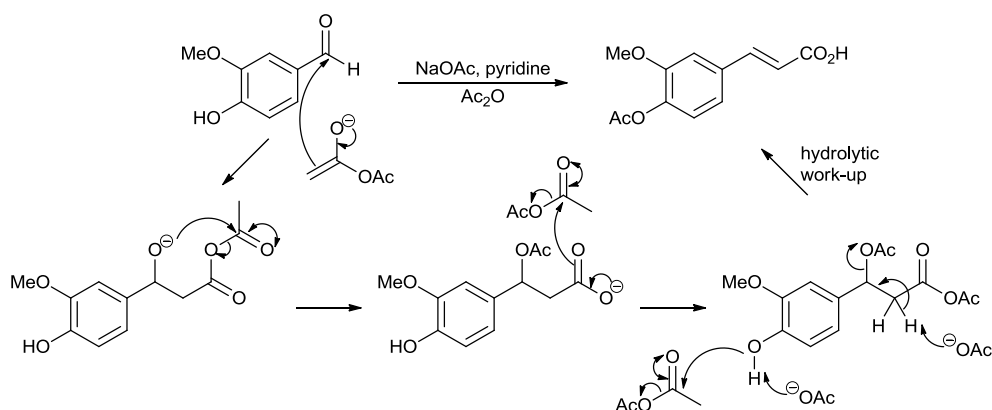
Scheme 10. An intramolecular aldol condensation reaction.

The Henry reaction follows a similar pathway and involves condensation of the anion of a nitroalkane with an aldehyde or ketone to afford a 2-nitroalkene. This reaction was used to install an α,β -unsaturated nitro fragment during Corey's synthesis of aspidophytine (Scheme 11).²⁹



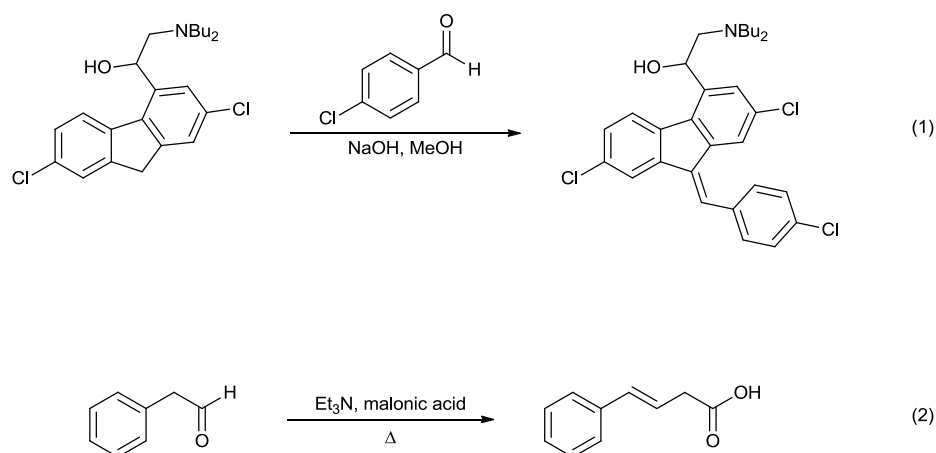
Scheme 11. The Henry reaction.

The Perkin reaction³⁰ utilises the enolate anion of a carboxylic acid anhydride as a nucleophile in a similar kind of condensation reaction. Reaction of the enolate of acetic anhydride, with a substituted benzaldehyde as the electrophilic partner, constitutes an efficient method for the synthesis of substituted (*E*)-cinnamic acids (Scheme 12).³¹



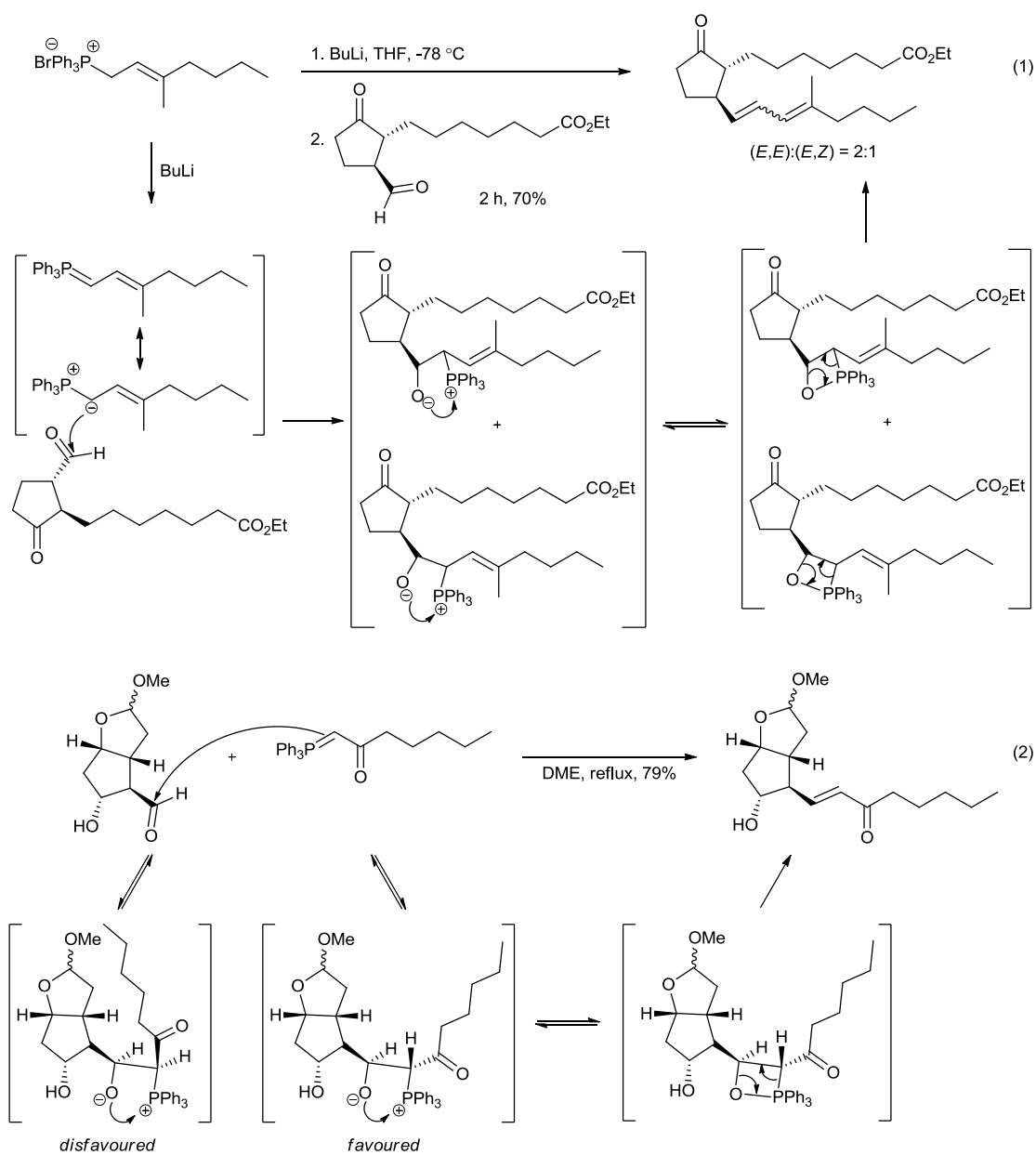
Scheme 12. The Perkin reaction.

Another variant of the aldol condensation reaction is the Knoevenagel condensation.³² An active methylene compound is first deprotonated, followed by 1,2-addition of the stabilised anion to an aldehyde or ketone and then elimination of water. This reaction has been used as a key step in the commercial production of the antimalarial drug lumefantrine (Scheme 13, eq 1).³³ The use of a malonate-derived anion as the nucleophile can allow for the selective preparation of γ,δ -unsaturated carboxyl compounds, *via* the subsequent loss of an acid group by decarboxylation (*vide infra*) (Scheme 13, eq 2).



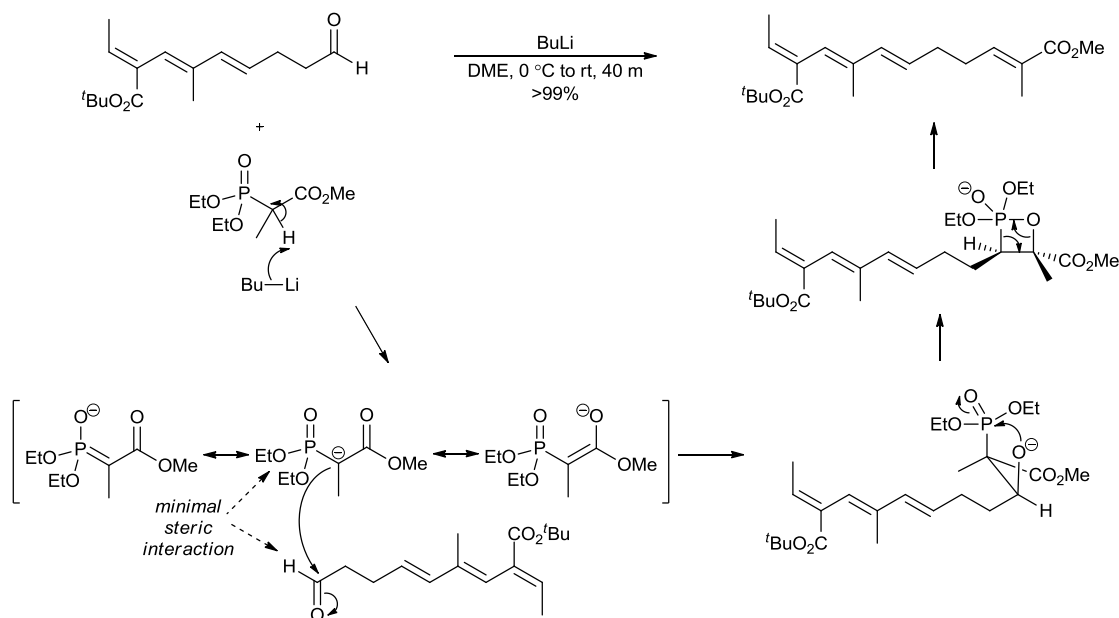
Scheme 13. Knoevenagel condensation reactions.

A well-established strategy for alkene synthesis is the Wittig reaction,³⁴ which consists of addition of a phosphorus-derived ylide to either an aldehyde or ketone, followed by elimination of phosphine oxide and alkene bond formation. The reaction is most efficient with aldehydes, although the product alkene is often formed as a mixture of geometric isomers (Scheme 14, eq 1).³⁵ However, if the ylide is stabilised by an electron-withdrawing group, the reversible nature of the reaction ensures that the alkene bond is formed with high selectivity for its thermodynamically more stable (*E*)-isomer (Scheme 14, eq 2).³⁶



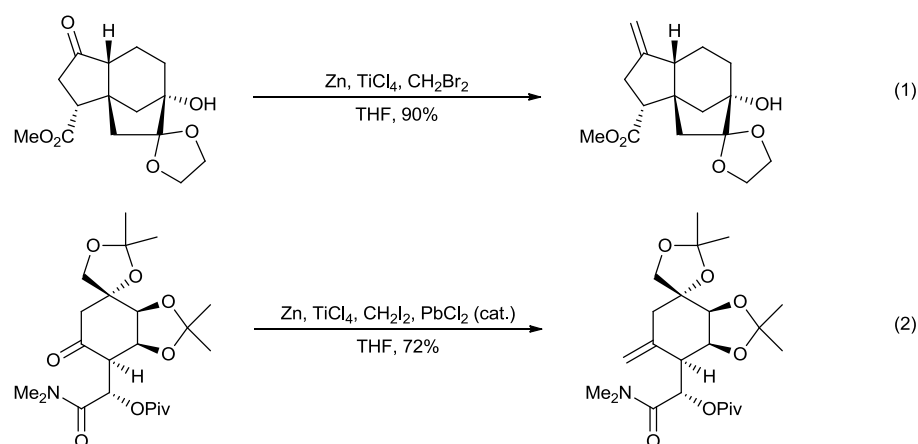
Scheme 14. The Wittig olefination reaction using non-stabilised (eq 1) and stabilised (eq 2) ylides.

The Horner-Wadsworth-Emmons variant of the Wittig olefination utilises a stabilised, phosphonate-derived ylide, and typically proceeds with an excellent level of stereoselectivity for the (*E*)-alkene product (Scheme 15).³⁷ In addition, the phosphorus byproduct is a water-soluble phosphate ester, which, unlike triphenylphosphine oxide, is easily separated from the post-reaction mixture on work-up.



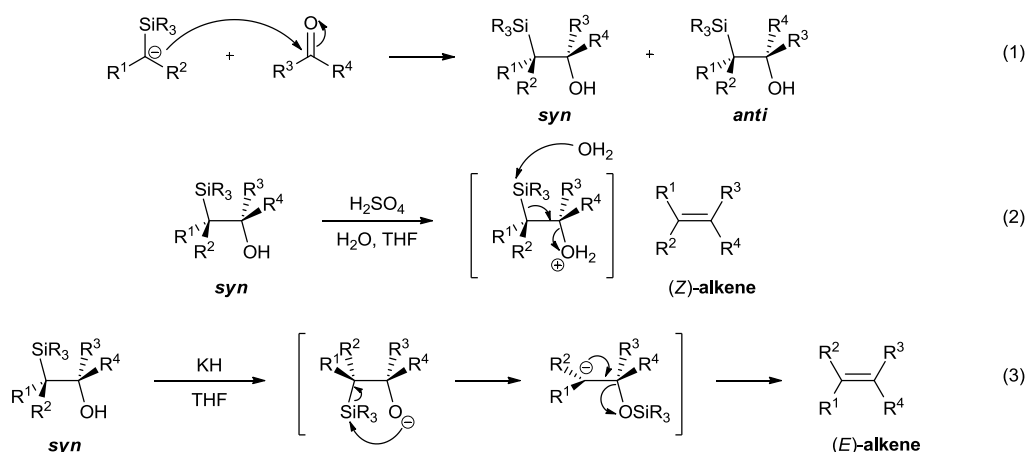
Scheme 15. Horner-Wadsworth-Emmons olefination reaction.

Another limitation of the Wittig reaction arises from its relatively slow reaction rate with ketones, with enolisation competing with the carbonyl addition, potentially resulting in epimerisation of adjacent stereocentres or enolate condensation reactions.³⁸ This led to the development of the Lombardo methylenation reaction (Scheme 16, eq 1),³⁹ whereby a highly nucleophilic species is prepared *via* addition of TiCl_4 to a suspension of zinc dust in a THF solution of dibromomethane, which reacts rapidly with aldehydes and ketones to afford their corresponding methylenated products. The remarkable functional group tolerance and non-basicity of the reagent permits its use in the presence of THP ethers, TBS ethers, acetals, esters, lactones, amides, carboxylic acids, unprotected alcohols and substrates containing potentially enolisable stereocentres. For example, this procedure was also utilised by Du Bois and co-workers during their synthesis of (–)-tetrodotoxin (Scheme 16, eq 2).⁴⁰



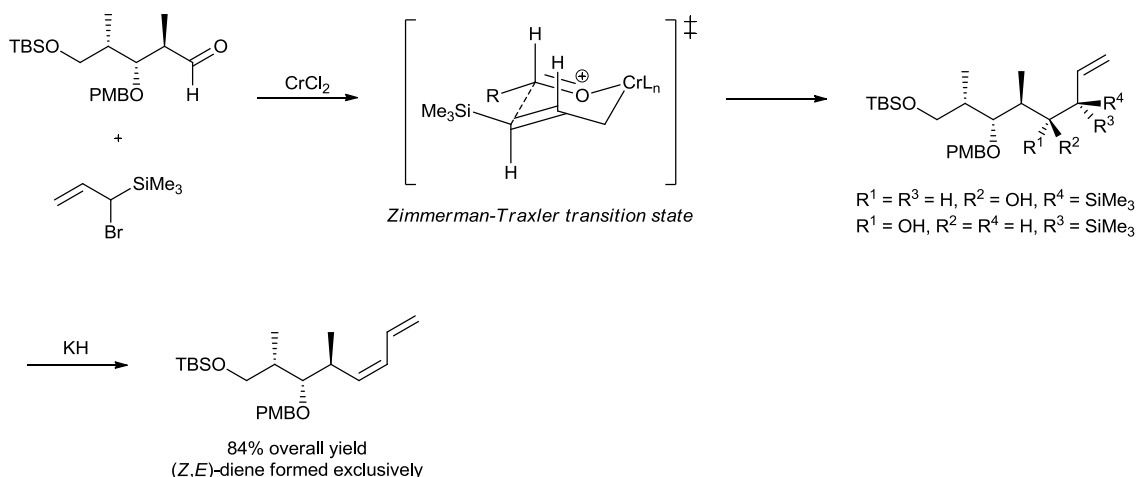
Scheme 16. The Lombardo methylenation reaction of ketones (eq 1) and an example of its use in natural product synthesis (eq 2).

Alkene synthesis can also be achieved *via* reaction of α -silyl carbanions with carbonyl compounds, as discovered by Peterson⁴¹ in 1968. The reaction pathway depends strongly upon the coordinating ability of the metal counterion associated with the silyl anion, whereby relatively ionic alkoxides (e.g. Na, K) result in direct elimination of the corresponding silanol with concomitant formation of an alkene bond. This pathway is also followed where R^1 or R^2 are electron-withdrawing groups. If the intermediate alkoxide-metal bond is relatively covalent and stabilised, then it may be protonated upon aqueous work-up and isolated (Scheme 17, eq 1).³ Subsequent treatment with either acid or base then results in stereoselective alkene formation *via* elimination of the trialkylsilanol. Interestingly, each diastereomer of the β -hydroxysilane (*syn/anti*) affords the opposing alkene geometric isomer upon treatment with either acid or base (Scheme 17, eqs 2 and 3, respectively).⁴²



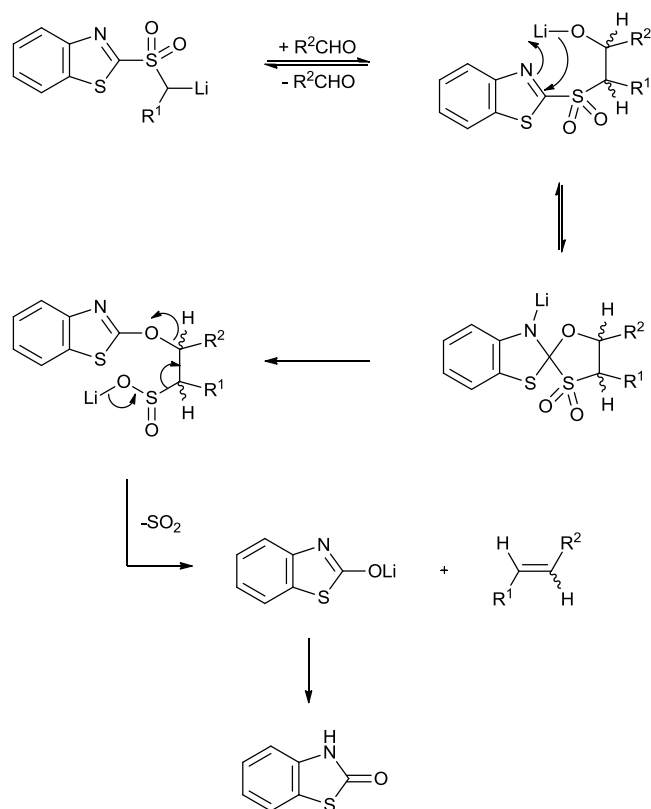
Scheme 17. Peterson olefination reaction.

Although separation of the intermediate β -hydroxysilanes enables geometrically pure alkenes to be isolated, the inefficiency of this separation step has resulted in this methodology not finding widespread application in synthesis. Consequently, alternative methods for the stereoselective preparation of these types of silyl products have been developed. For example, Nozaki-Hiyama allylation of an aldehyde gave a β -hydroxysilane with excellent stereocontrol, which was followed by a Peterson-type elimination to afford a fragment of use for the total synthesis of (+)-discodermolide (Scheme 18).⁴³



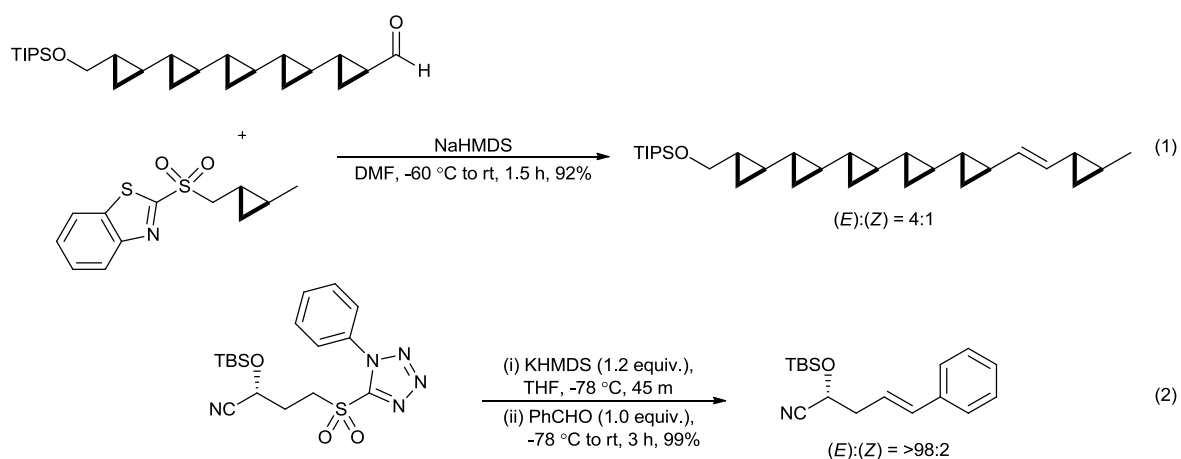
Scheme 18. Diastereoselective β -hydroxysilane formation, followed by Peterson elimination reaction.

In 1991, a new one-pot preparation of alkenes from reactions of lithiated 2-benzothiazolyl sulphones with aldehydes or ketones was reported by Julia and co-workers.⁴⁴ Initial 1,2-addition of a sulphone-derived carbanion to a carbonyl group is followed by a cascade of reactions that ultimately results in alkene formation and elimination of sulphur dioxide (Scheme 19). Unfortunately, high stereoselectivities could only be achieved for a narrow range of substrates, whilst many lithiated benzothiazolyl sulphones were found to be unstable. An investigation into the effects of base, solvent polarity, heterocyclic sulphone and branching in the aldehyde and sulphone precursors was later undertaken by Kocienski and co-workers.⁴⁵ They found that alkylated 1-phenyl-1*H*-tetrazol-5-yl sulphones delivered superior stereoselectivities when compared to other heterocyclic sulphones, with the geometric purity of the alkene product being maximised by the use of a potassium base and a strongly coordinating solvent.



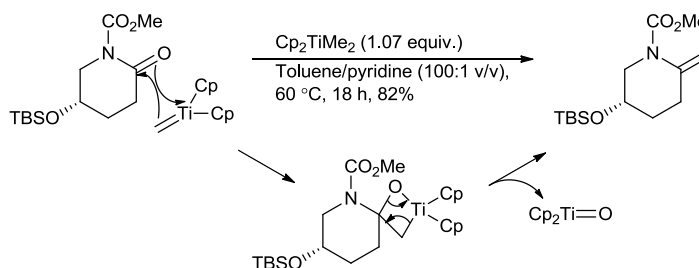
Scheme 19. Proposed mechanism of the Julia-Kocienski olefination.

In general, formation of an (*E*)-alkene product is favoured; however, some combinations of solvent, base, sulphone and aldehyde can favour the (*Z*)-alkene. The Julia-Kocienski olefination thereby constitutes an effective alternative to the Wittig reaction for the stereoselective synthesis of 1,2-disubstituted alkenes (Scheme 20, eqs 1 and 2).^{46,47}



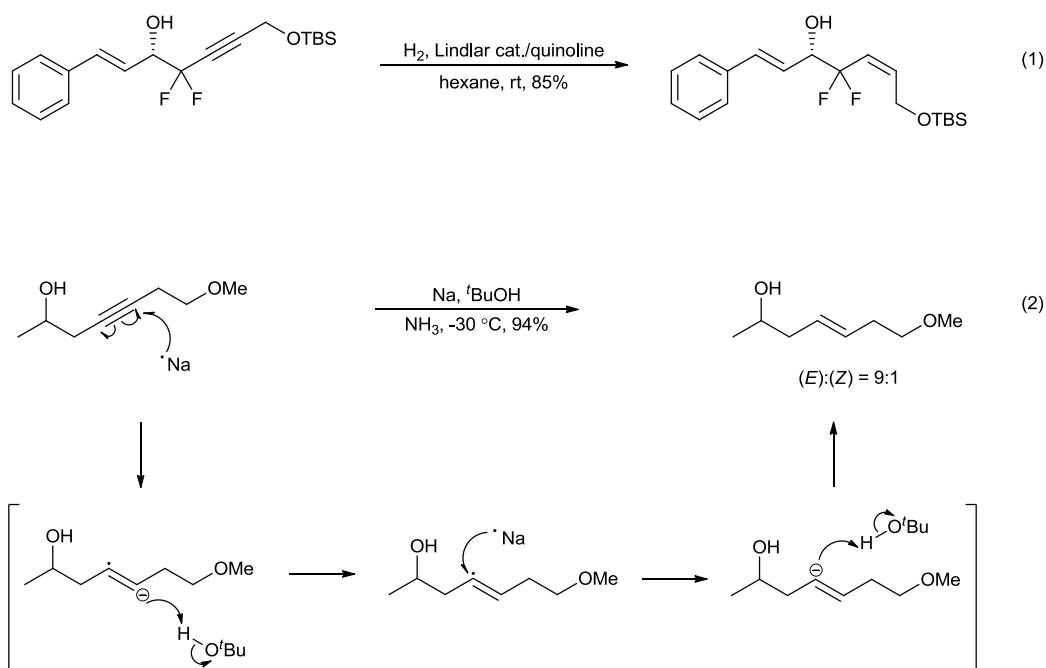
Scheme 20. The Julia-Kocienski olefination reaction.

The transformation of esters and amides into their corresponding enol ethers and enamines cannot be achieved *via* Wittig or Julia olefination reactions. In order to carry out this type of conversion, a range of titanium-based reagents have been developed. For example, the titanium methylide complex $\text{Cp}_2\text{Ti}=\text{CH}_2$, generated *in situ* by thermal decomposition of dimethyltitanocene, can be used to methylenate various amides, esters and imides (Scheme 21).^{48,49}



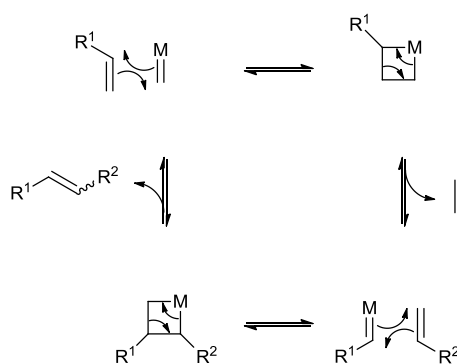
Scheme 21. Methylenation of an imide carbonyl group using dimethyltitanocene.

1,2-Disubstituted and terminal alkenes can also be prepared by the partial reduction of alkynes, where selectivity for either geometric isomer can be readily achieved by the use of appropriate reaction conditions. The semi-hydrogenation of internal alkyne substrates, using a transition metal-based catalyst and hydrogen gas can afford a (*Z*)-alkene product in up to 100% selectivity. The catalyst most often utilised for this purpose is known as the Lindlar catalyst,⁵⁰ which is comprised of palladium metal deposited onto a calcium carbonate support that has been ‘poisoned’ by treatment with lead(II) acetate. The inclusion of small amounts of quinoline in the hydrogenation reaction mixture is also known to improve catalyst selectivity. This procedure was utilised during the synthesis of *gem*-difluorinated goniiothalamins reported by Qing and co-workers (Scheme 22, eq 1).⁵¹ Alternatively, the use of dissolving metal reductions can result in the selective formation of (*E*)-alkenes *via* a single electron transfer process. For example, the use of sodium metal in liquid ammonia with *tert*-butanol as a proton quench was reported to afford the desired (*E*)-isomer with 90% selectivity (Scheme 22, eq 2).⁵²



Scheme 22. Alkene synthesis *via* the partial reduction of alkynes, to afford (Z)- or (E)-alkenes.

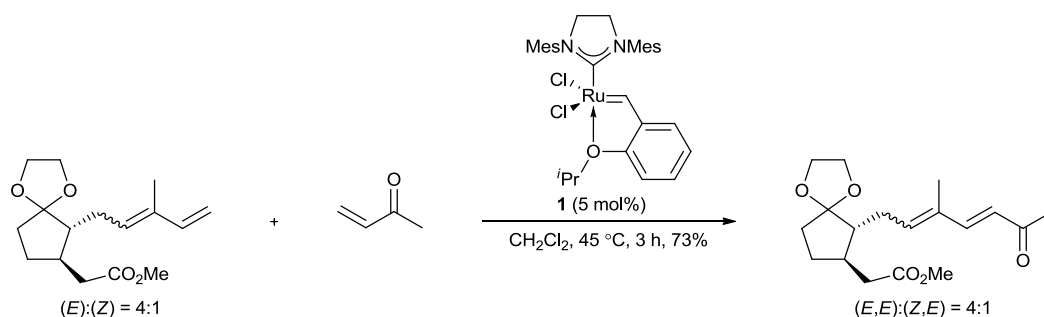
Since the introduction of well-defined, stable, reactive and functional group tolerant metathesis catalysts, catalytic alkene metathesis has emerged as a powerful synthetic tool.⁵³ In this unique reaction, two alkenes are effectively “stitched together” *via* an exchange of alkene substituents, thus facilitating the efficient and rapid generation of molecular complexity. A simplified mechanism for this type of cross-coupling reaction is shown in Scheme 23.



Scheme 23. Mechanism of alkene cross-metathesis catalysed by a metal carbene, $M=CH_2$.

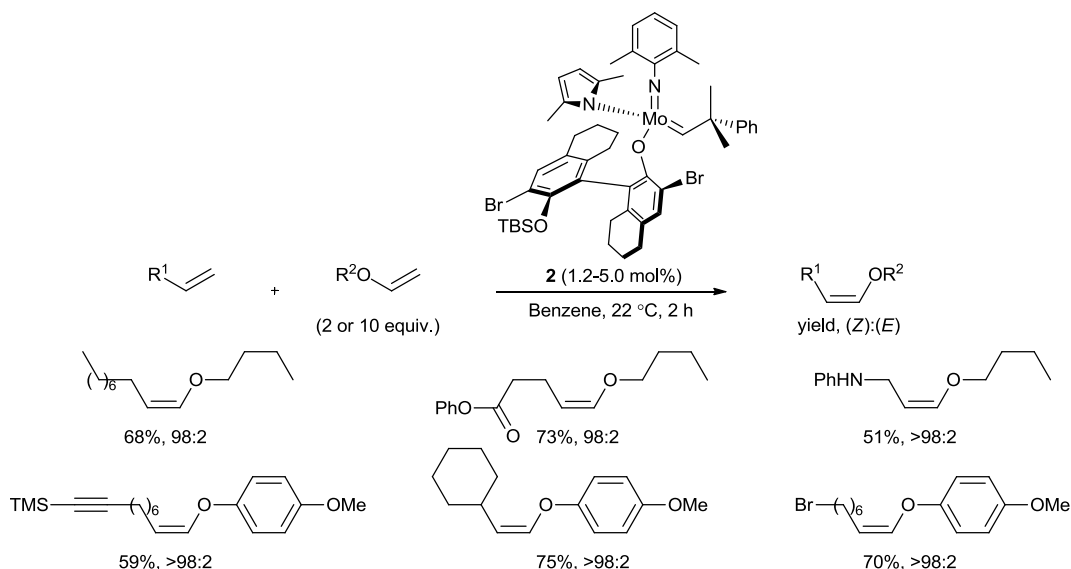
Alkene metathesis reactions can be broadly classified into three main classes: cross-metathesis (CM), ring-opening metathesis (ROM) and ring-closing metathesis (RCM). Although the overall synthetic outcome of these processes can be achieved using other

synthetic methodology, the metathesis approach is often superior in terms of efficiency, selectivity and favourable byproduct formation (e.g., ethylene gas). For example, the cross-metathesis of methyl vinyl ketone with various terminal dienes reported by Blechert⁵⁴ occurs readily to afford dienone products (Scheme 24), where the presence of both acid- and base-sensitive functionality in the substrate would preclude the use of many alternative preparations.



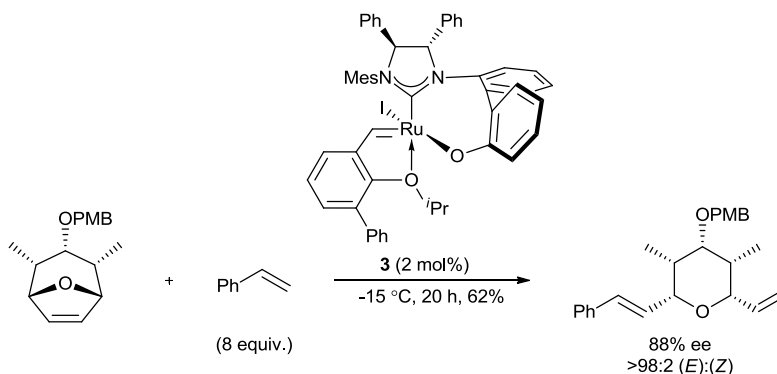
Scheme 24. Cross-metathesis of methyl vinyl ketone with a terminal diene.

Although cross-metathesis is a highly reliable method for C=C bond formation, the (*E*)-alkene isomer is normally favoured due to the lower thermodynamic stability of (*Z*)-alkenes.⁵⁵ Examples of (*Z*)-selective cross-metathesis are mainly limited to substrates featuring *sp*-hybridised substituents, such as acrylonitrile⁵⁶ or enynes.⁵⁷ However, Hoveyda, Schrock and co-workers⁵⁸ have recently reported the synthesis and impressive selectivity of a molybdenum-based catalyst **2**, which was used for the (*Z*)-selective cross-metathesis of either aliphatic or aromatic enol ethers with a range of terminal alkenes under kinetic control (Scheme 25).



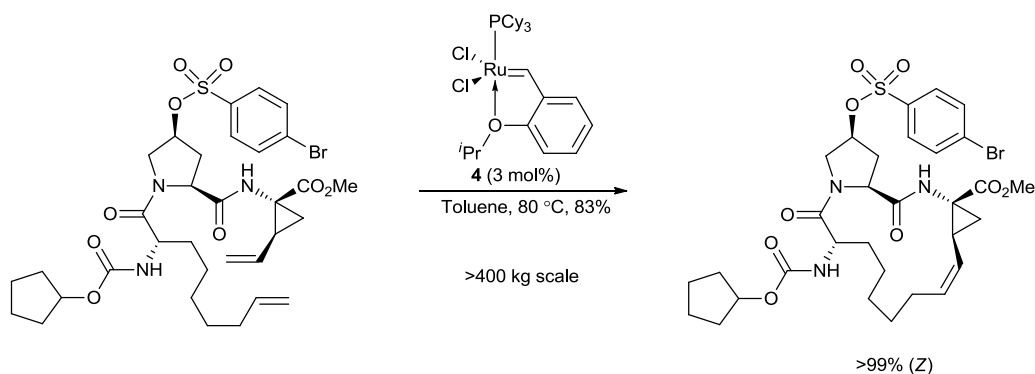
Scheme 25. Highly (*Z*)-selective cross-metathesis between enol ethers and terminal alkenes.

Where applicable, enantioselective variants of each class of metathesis reaction have been reported.⁵⁹ In the following example of a ring-opening/cross-metathesis reaction, the chiral catalyst **3** efficiently discriminates between the enantiotopic ends of the substrate alkene to form a cross-metathesised product in high enantiomeric excess (Scheme 26).⁶⁰



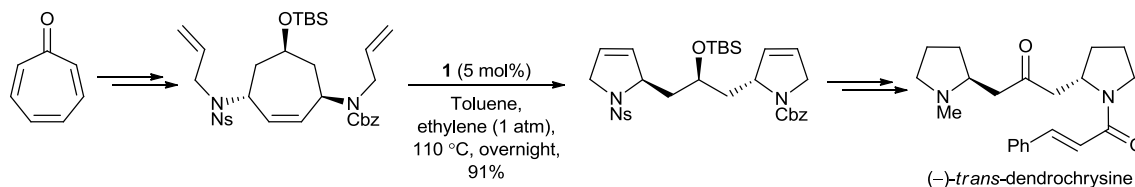
Scheme 26. Enantioselective ring-opening/cross-metathesis using a chiral ruthenium alkylidene complex.

Ring-closing metathesis allows ready access to all ring sizes ≥ 5 and has thus found frequent application in the field of natural product synthesis.⁶¹ It also constitutes a highly versatile method for preparing medium-to-large ring systems. An illustrative example is the ring-closing metathesis step utilised by Boehringer Ingelheim for the multi-kilogram synthesis of BILN-2061,⁶² an antiviral drug candidate which has since been discontinued due to toxicity issues. This ring-closure reaction was catalysed by the second-generation Grubbs-Hoveyda catalyst **4**, proceeding cleanly in high yield and with almost complete selectivity for the (Z)-alkene (Scheme 27).



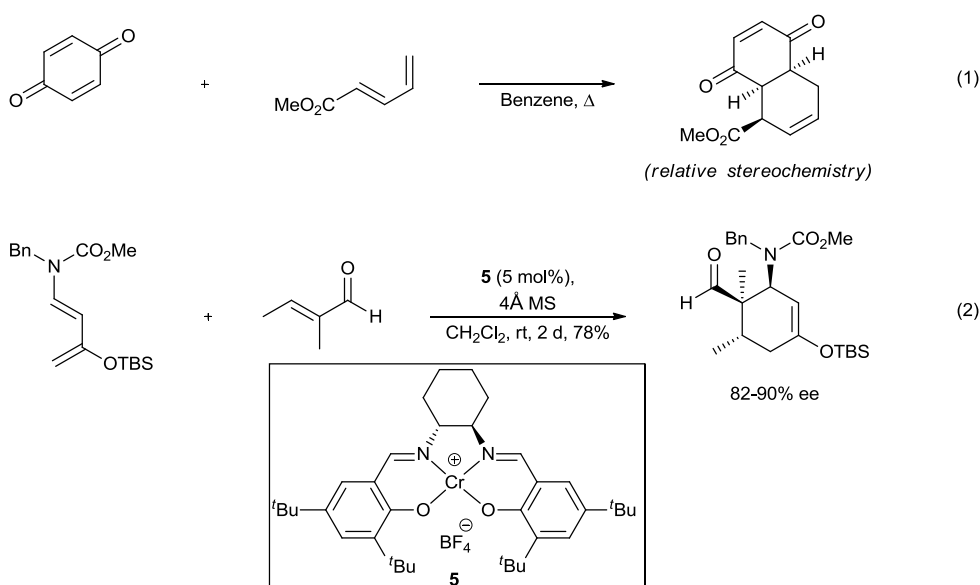
Scheme 27. Ring-closing metathesis reaction on a large scale.

A relatively new class of metathesis reaction is ring-rearrangement metathesis (RRM),⁶³ which consists of sequential ring-opening and ring-closing metathesis steps. The synthetic relevance of this reaction is demonstrated by its application to the first stereoselective total synthesis of (–)-*trans*-dendrochrysine, reported in 2007 by Blechert.⁶⁴ The RRM substrate was prepared in several steps from cycloheptatrienone, whereupon the cycloheptene ring was smoothly transformed into a pair of dihydropyrrole units, with complete conservation of enantiopurity, using the Grubbs-Hoveyda second generation catalyst **1** (Scheme 28).



Scheme 28. Synthesis of (–)-*trans*-dendrochrysine via a ring-rearrangement metathesis reaction.

Another powerful method for the synthesis of cyclic alkenes is the Diels-Alder reaction,⁶⁵ which is a thermally allowed, [4+2] cycloaddition reaction between a diene and dienophile. This reaction has been frequently and consistently utilised for the synthesis of natural products, for example in Woodward's 1956 synthesis of reserpine (Scheme 29, eq 1).⁶⁶ Enantioselective variants have since been developed, using various forms of organocatalysis⁶⁷ or chiral Lewis-acidic transition metal-based catalysts.⁶⁸ For example, the chromium(III) salen complex **5** was used to catalyse an enantioselective Diels-Alder reaction during Hsung's study of the total synthesis of (–)-phomactin A (Scheme 29, eq 2).⁶⁹



Scheme 29. Synthetic applications of the Diels-Alder reaction.

1.3 Conclusion

It is clear from this brief discussion that a wide range of synthetic methodology has been developed for the stereoselective synthesis of alkene bonds in the presence of a wide range of chemical functionality. A less well exploited approach for the synthesis of alkenes involves the use of a transition metal catalyst to isomerise a pre-existing alkene bond, thus affording a new geometric or positional isomer; this area will now be comprehensively reviewed in the following chapter.

2. Alkene isomerisation strategies

Alkene isomerisation reactions have often been encountered as undesired side-reactions during asymmetric catalytic hydrogenation⁷⁰ or metathesis reactions,⁷¹ that have the potential to compromise enantioselectivity and promote the formation of byproducts. However, the deliberate and controlled isomerisation of a pre-existing alkene bond can potentially afford positional and geometric isomers that are difficult to prepare using conventional methodology. Established methods for carrying out this type of transformation include: treatment of an easily prepared alkene substrate with radicals,⁷² boranes,⁷³ halogens,⁷⁴ strong acids⁷⁵ and bases.⁷⁶ However, there are many disadvantages associated with these methods due to functional group incompatibility with the harsh reaction conditions that are often required for isomerisation to occur. Photochemical methods have been applied to the (*E*)/(*Z*)-isomerisation of alkenes,⁷⁷ but the success of this approach is substrate dependent, with mixtures of products often being produced. Although additional cycles of reaction and separation can result in high yields of a pure geometric isomer, this is a tedious process that is often unfeasible on a preparative scale.

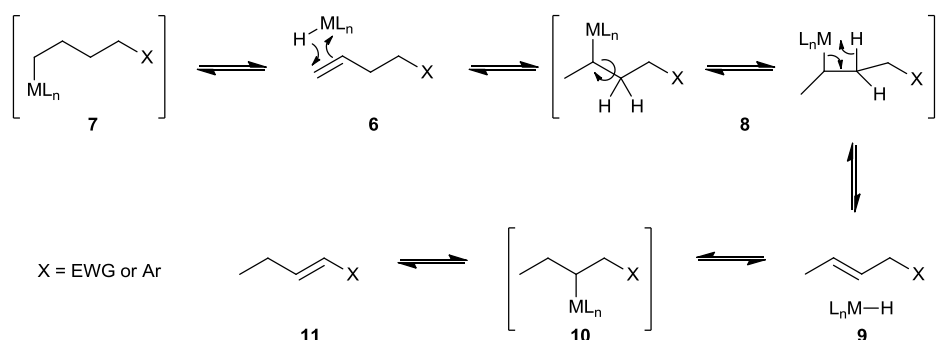
The use of transition metal-based catalysts offer several advantages over these more conventional methods, such as functional group tolerance, mild reaction conditions, product selectivity and tunability (e.g., where homogeneous catalysts are used, variation of ligands is possible). From an industrial perspective, catalytic processes are infinitely more desirable than those that employ reagents in stoichiometric quantities, as product separation is greatly simplified. This is especially advantageous for the synthesis of pharmaceutical compounds intended for human consumption, which must adhere to strict purity requirements. The use of a catalyst also results in significantly lower quantities of waste material being generated, leading to greater economic efficiency, particularly on a large scale. A quantitative isomerisation reaction can potentially furnish the desired product in a 100% atom-economical manner,⁷⁸ which clearly adheres to the principles of green chemistry.

The following literature review will now provide a focused overview of synthetically useful alkene isomerisation reactions that have been carried out using transition metal catalysts, beginning with a brief mechanistic discussion of transition metal-catalysed alkene isomerisation pathways.

2.1 Mechanisms of transition metal-catalysed alkene isomerisation

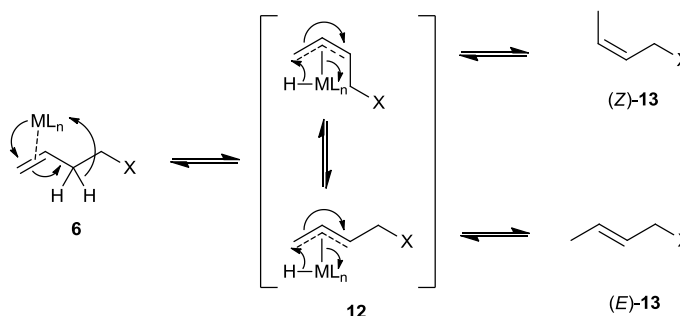
The vast majority of alkene isomerisation reactions mediated by transition metal-based catalysts proceed *via* either of the following mechanisms: (1) Reversible addition-elimination of a metal hydride species to an alkene functionality to give a thermodynamically more stable geometric or positional isomer, or (2) formation and rearrangement of a π -allylmetal hydride complex using a metal catalyst that contains at least two vacant coordination sites.^{79,80}

A representative addition-elimination mechanism involving treatment of a terminal, linear alkene **6** with a generic metal hydride species L_nM-H is shown in Scheme 30. A reversible hydrometalation reaction occurs *via* coordination of the alkene functionality of **6** to the metal followed by reversible *syn*-addition of a metal hydride species across the alkene bond. If addition occurs in an *anti*-Markovnikov fashion to afford intermediate **7**, it will position the metal species at the terminal position, with subsequent elimination of the metal hydride species resulting in reversion to starting alkene **6**. However, a Markovnikov addition pathway will afford intermediate **8** that can either eliminate a metal hydride species to afford starting material **6**, or undergo an alternative hydrogen elimination pathway from its 3-position to afford a 2-alkenyl product **9**. Elimination of the metal hydride species **8** can occur *via syn*-periplanar conformers leading to either an (*E*)- or (*Z*)-alkene, with any of the less stable (*Z*)-isomer formed being isomerised to its (*E*)-isomer by further rounds of addition-elimination reactions of metal hydride species. Further reversible addition-elimination reaction of $M-H$ species may also occur to afford new positional alkene isomers such as **11**, *via* pathways that are particularly favoured if the new alkene product **11** is conjugated to an electron-withdrawing group or aromatic ring.



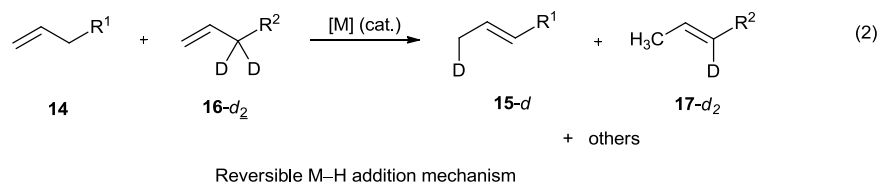
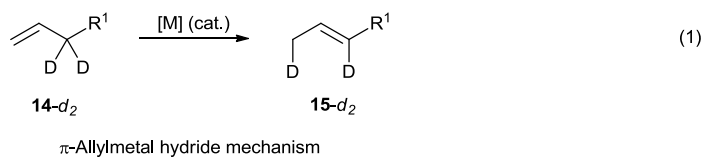
Scheme 30. Addition-elimination mechanism of transition metal-catalysed alkene isomerisation.

An alternative π -allylmetal hydride mechanism for alkene isomerisation is shown in Scheme 31. Initial complexation of alkene **6** to the catalyst ML_n is followed by reversible hydride abstraction from the allylic position of the complex to afford a π -allylmetal hydride species **12**. The allyl fragment of this intermediate can readily interconvert between *syn*- and *anti*-conformations, with the position of the equilibrium being dependent on steric factors and/or nature of the ligands coordinated to the metal centre. Intramolecular delivery of hydride to the terminal end of the allyl fragment can then occur, which results in migration of the alkene bond to afford an internal prop-2-enyl alkene bond, with an (*E*)-**13** isomer generally predominating under thermodynamic control. The alkene bond of **13** can also undergo further isomerisation reactions, however when the alkene contains a good allylic leaving group (e.g., acetate, halide) then competing reactions of cationic π -allyl intermediates with adventitious nucleophiles can occur.⁸¹



Scheme 31. The π -allylmetal hydride mechanism of transition metal-catalysed alkene isomerisation.

Differentiation between these two mechanisms is often difficult, although this has been achieved by studying reactions of appropriately labelled substrates.⁸² For example, isomerisation of a deuterated 1-alkene **14-d₂** with a metal catalyst that proceeds *via* a π -allylmetal hydride mechanism would result in clean transfer of deuterium to the termini of the 2-alkene product **15-d₂** (Scheme 32, eq 1).⁸³ Further evidence may also be obtained through carrying out crossover experiments⁸⁴ as no intermolecular migration of deuterium between **14** and **16-d₂** would be expected for a π -allylmetal hydride mechanism, however a reversible metal hydride addition mechanism would be expected to result in some scrambling of deuterium between the two isomerisation products (Scheme 32, eq 2).⁸⁵

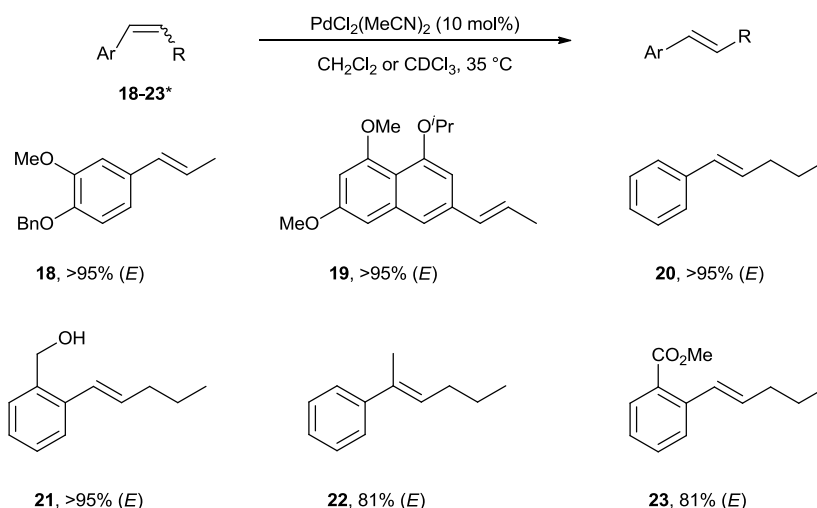


Scheme 32. Eq 1: Isomerisation of a deuterium-labelled substrate that proceeds *via* a π -allylmetal hydride mechanism; Eq 2: Isomerisation of a deuterium-labelled substrate that proceeds *via* a reversible metal hydride addition mechanism.

2.2 (*E*)/(*Z*)-Isomerisation of alkenes

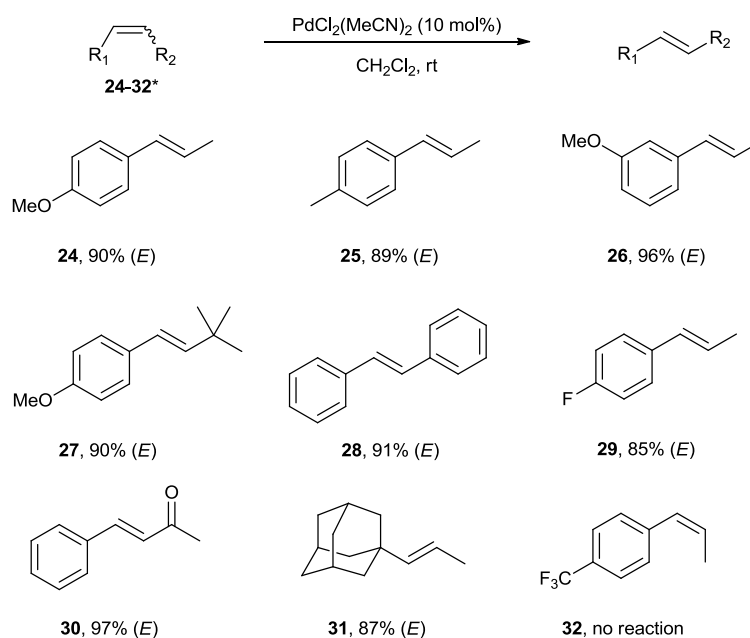
Many of the synthetically useful alkene bond forming reactions discussed in the previous chapter can result in olefinic products as unwanted mixtures of (*E*)- and (*Z*)- geometric isomers that are difficult to separate. Although variants of these methodologies have been developed that proceed with high levels of stereocontrol,^{42,86,87} the availability of isomerisation protocols that enable the selective conversion of (*Z*)-alkenes into their thermodynamically more stable (*E*)-isomers can improve the efficiency of many of these protocols. It is known that alkene isomers can be interconverted *via* treatment with certain transition metal complexes, thus providing a mild method for isomerisation of (*Z*)-olefins to their corresponding (*E*)-isomers in both acyclic and medium/large ring systems. These isomerisation protocols only produce good yields of (*E*)-alkenes if competing alkene *migration* pathways can be efficiently suppressed, otherwise complex mixtures of positional isomers are also produced.^{88,89} Consequently, good yields of (*E*)-geometric isomers are generally only obtained for isomerisation of (*Z*)-aryl-substituted alkenes, or (*Z*)- α,β -unsaturated carbonyl compounds, where conjugation ensures that the position of the alkene bond is retained in the product.

Palladium(II) complexes have proven to be the most widely used class of catalyst for carrying out (*Z*)-/(*E*)- isomerisation reactions, with Giles and co-workers reporting the first synthetically useful protocol in 1990.⁹⁰ They employed a series of Wittig reactions to prepare mixtures of (*E*)/(*Z*)-aryl-alkenes (predominantly (*Z*)-) (**18-23**, Scheme 33) that were subsequently isomerised into their corresponding (*E*)-isomers in good yield using a catalytic amount of PdCl₂(MeCN)₂ in CH₂Cl₂ or CDCl₃ at 35 °C. However, application of this isomerisation procedure to a mixture of (*E*)- and (*Z*)-4-octene was not successful, resulting in competing alkene migration reactions occurring to afford a complex mixture of regioisomeric octenes. In 2002, Spencer and co-workers⁹¹ further explored the use of PdCl₂(MeCN)₂ (10 mol%) as a catalyst for the isomerisation of various (*Z*)-aryl-alkenes, a (*Z*)- α,β -unsaturated ketone and a (*Z*)-alkene containing a quaternary allylic centre (Scheme 34), reporting >85% isolated yields of their corresponding (*E*)-alkenes in all cases. However, propenylbenzene **32**, which has a CF₃-substituent in its *para*-position, failed to react under these conditions.



*Wittig reactions used to prepare alkenes **18-23** as (*E*)/(*Z*)-mixtures

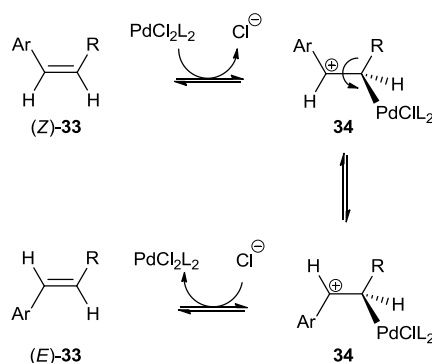
Scheme 33. $\text{PdCl}_2(\text{MeCN})_2$ catalysed (*Z*)-to-(*E*) isomerisation of substituted styrenes.



*Wittig reactions used to prepare alkenes **24-32** as (*E*)/(*Z*)-mixtures

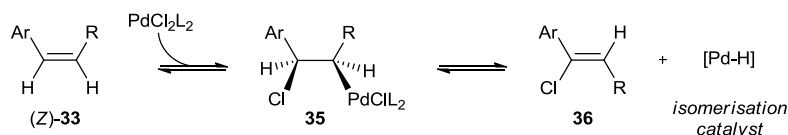
Scheme 34. Scope of $\text{PdCl}_2(\text{MeCN})_2$ catalysed (*Z*)-to-(*E*) isomerisation reaction.

Spencer and co-workers have proposed that alkene isomerisation proceeds *via* reversible addition of $\text{PdCl}_2(\text{MeCN})_2$ to an alkene bond to give a carbocation intermediate **34** that rotates around its central carbon-carbon σ -bond to provide a pathway for interconversion of its (*E*)- and (*Z*)-isomers under thermodynamic control (Scheme 35).



Scheme 35. Carbocation mechanism for $\text{PdCl}_2(\text{MeCN})_2$ -catalysed (*E*)/(*Z*)-isomerisation reactions of 3-substituted (*Z*)-1-arylpropenes.

However, this mechanism does not explain the ability of this class of catalyst to isomerise aryl-allyl substrates to their corresponding prop-2-enyl regioisomers. Therefore, we propose these type of (*Z*)/(*E*)-isomerisation reactions are likely to be facilitated by a palladium hydride species Pd-H , that could be generated *in situ* from elimination of intermediate **35** (Scheme 36).



Scheme 36. Formation of a palladium hydride species.

This palladium complex and the bis(benzonitrile) analogue $[\text{PdCl}_2(\text{PhCN})_2]$ have since been frequently utilised to isomerise mixtures of (*Z*)- and (*E*)-arylalkenes that were generated as isomeric mixtures in unselective alkene bond-forming reactions (see Figure 2).

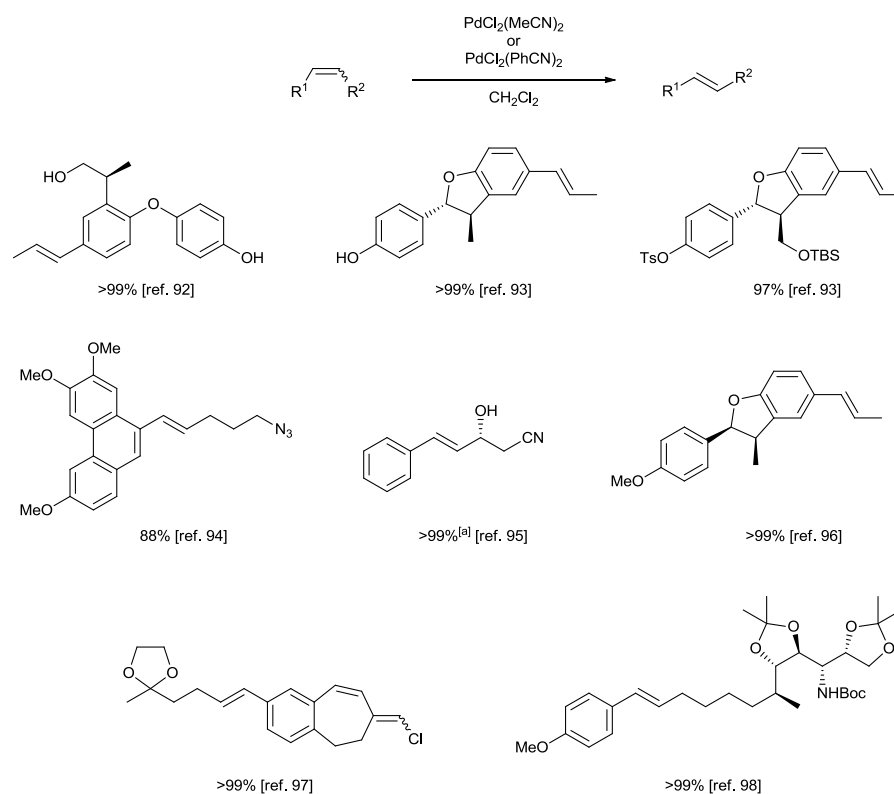
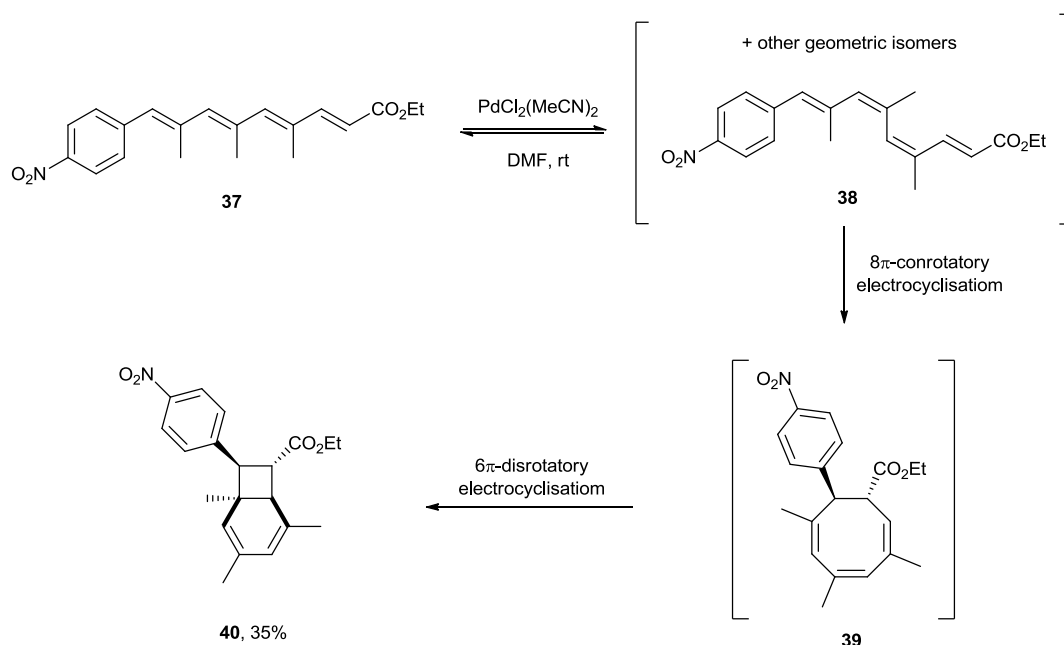


Figure 2. Mixtures of $(E)/(Z)$ -alkenes that were subsequently isomerised to their corresponding (E) -isomers using $\text{PdCl}_2(\text{MeCN})_2$ or $\text{PdCl}_2(\text{PhCN})_2$.

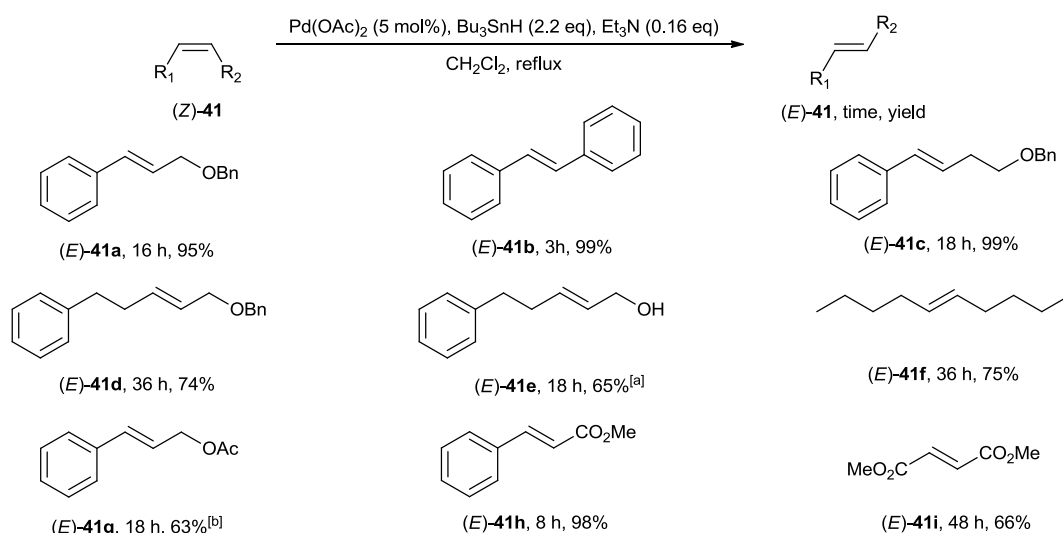
[a] The isomerisation reaction was carried out in refluxing benzene.

Palladium(II) complexes have also been used to catalyse multiple $(Z)/(E)$ -isomerisation reactions of polyenes, enabling access to geometric isomers that would otherwise be difficult to obtain. Baldwin and co-workers have elegantly employed palladium-catalysed isomerisation reactions of conjugated polyenes as a key transformation in their biomimetic syntheses of bicyclic cyclobutane derived frameworks (Scheme 37).^{99,100,101} For example, they showed that $\text{PdCl}_2(\text{MeCN})_2$ could be used to generate an equilibrating mixture of isomeric tetraalkenes from an isomerically pure (E,E,E,E) -tetraene precursor **37**, with the (E,Z,Z,E) -isomer **38** possessing the required alkene geometry to undergo a series of tandem electrocyclization reactions to afford the desired bicyclic [4.2.0] cyclobutane framework **40**.



Scheme 37. $\text{PdCl}_2(\text{MeCN})_2$ mediated isomerisation results in formation of (E,Z,Z,E) -tetraene **38** that reacts *via* a series of electrocyclic ring closure reactions to afford bicyclobutane **40**.

Other isomerisation protocols have recently been developed for the selective conversion of (Z) -alkenes into their corresponding (E) -isomers that are proposed to proceed *via* palladium(0) intermediates. Isomerisation of a range of (Z) -aryl-substituted alkenes and (Z) - α,β -unsaturated esters was achieved using a catalytic quantity of palladium(II) acetate in the presence of tributyltin hydride and triethylamine (Scheme 38).¹⁰² Although the highest conversions were obtained for substituted styrene derivatives, good yields were also achieved with substrates containing non-conjugated alkene bonds. Particularly impressive was the selective conversion of (Z) -4-decene to (E) -4-decene in 75% isolated yield, with very little alkene migration having taken place.

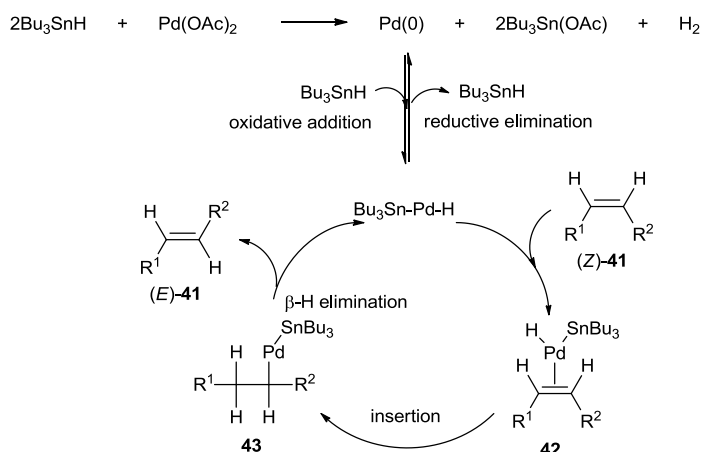


Scheme 38. Palladium-catalysed isomerisation of (*Z*)-alkenes using Bu_3SnH as a co-catalyst.

[a] 22% yield of a terminal alkene arising from elimination of the terminal hydroxyl group also formed.

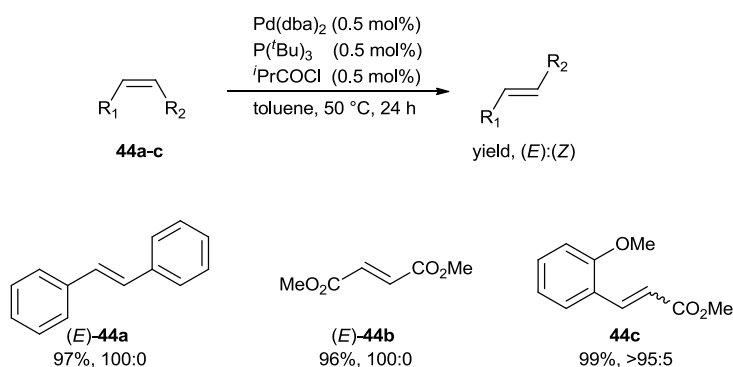
[b] 15% yield of internal and terminal alkenes also formed upon elimination of acetate.

The reaction pathway for these isomerisation reactions is proposed to involve tributyltin hydride mediated reduction of Pd(OAc)_2 to afford a palladium(0) species that inserts into a tin-hydrogen bond to afford a palladium hydride species Bu_3SnPdH (Scheme 39). Hydropalladation of the (*Z*)-alkene coordinated complex **42** then occurs to form alkylpalladium species **43**, with rotation around its carbon-carbon bond and subsequent β -hydrogen elimination affording the more thermodynamically stable alkene (*E*)-**41**, with regeneration of palladium hydride species Bu_3SnPdH completing the catalytic cycle.



Scheme 39. Proposed mechanism of palladium-catalysed isomerisation of (*Z*)-alkenes in the presence of tributyltin hydride and triethylamine.

Skrydstrup¹⁰³ has recently described the application of a highly effective low loading palladium(0) catalytic system comprised of a 1:1:1 ratio of Pd(dba)₂, P(^{*t*}Bu)₃, and isobutyryl chloride for the isomerisation of double bonds with excellent functional group tolerance. It was shown that this highly promising protocol generates a catalytically active palladium hydride species *in situ*, that cleanly isomerises the alkene functionalities of (*Z*)-stilbene (**44a**), dimethyl maleate (**44b**) and (*Z*)- α,β -unsaturated ester **44c** to afford their corresponding (*E*)-isomers in >95% isomeric purity, respectively (Scheme 40).



Scheme 40. (*Z*)-to-(*E*) isomerisations of some representative alkenes using an *in-situ* generated, bulky palladium hydride catalyst.

Finally, a rare example of the selective isomerisation of an (*E*)-alkene to its less thermodynamically stable (*Z*)-alkene counterpart was reported in 2009 by Zaera.¹⁰⁴ Treatment of (*E*)-2-butene with a supported platinum catalyst, consisting largely of tetrahedral platinum nanoparticles featuring exposed (111) facets, resulted in selective formation of (*Z*)-2-butene. Although a practically useful synthetic procedure was not reported, the fact that such contra-thermodynamic selectivity could be achieved has significant implications.

In conclusion, transition metal catalysis offers great potential for carrying out (*Z*)-to-(*E*) alkene isomerisation reactions under mild chemoselective conditions.

2.3 Isomerisation of substituted alkenes

2.3.1 Isomerisation of monosubstituted alkene substrates

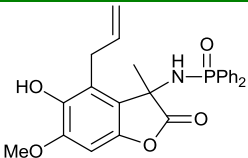
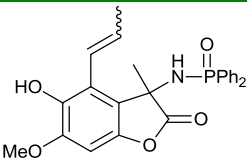
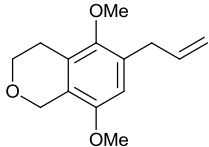
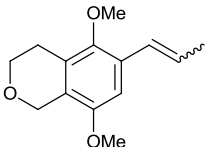
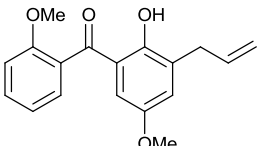
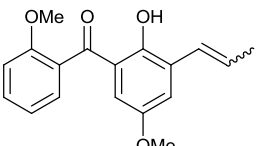
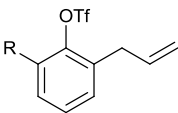
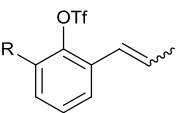
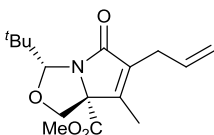
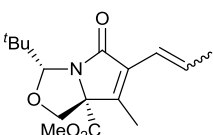
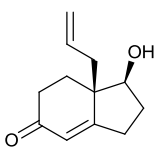
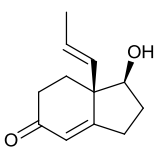
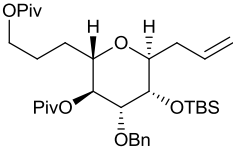
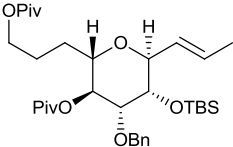
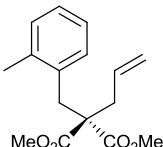
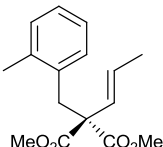
Hydrated rhodium(III) chloride (the anhydrous form is not isomerisation active) has been extensively used to isomerise a wide variety of alkenes featuring different substitution patterns and functional groups. Upon heating in an alcoholic solvent, typically ethanol, a rhodium hydride species is generated according to the following equation:^{105,106}

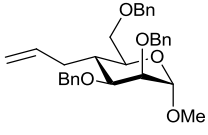
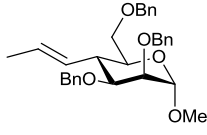
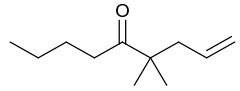
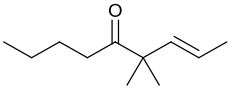
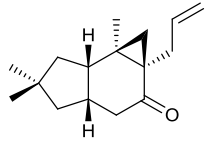
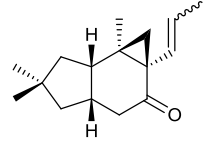
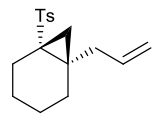
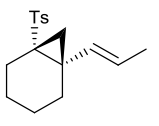
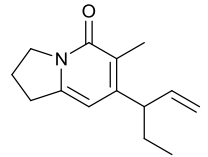
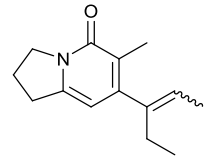
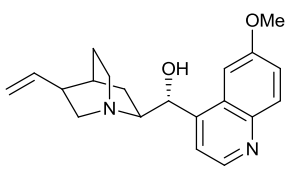
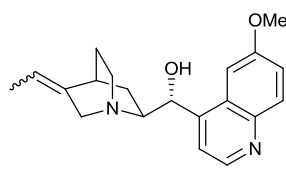


The rhodium hydride species thus formed is a highly reactive alkene isomerisation catalyst, with selected examples of isomerisation reactions of terminal alkenes that contain a wide range of functional groups shown in Table 1.

Table 1. Examples of rhodium trichloride-catalysed isomerisation reactions of monosubstituted alkenes to their disubstituted counterparts.

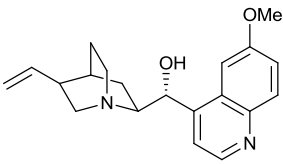
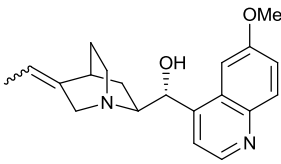
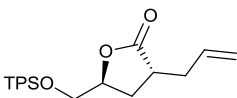
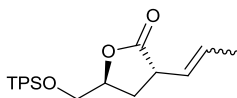
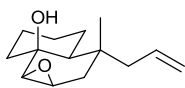
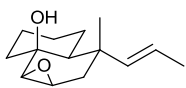
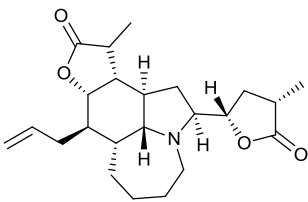
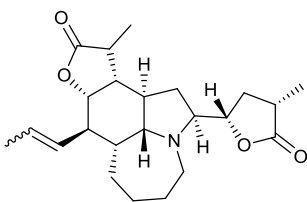
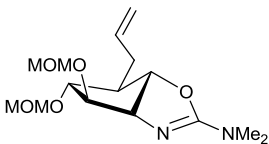
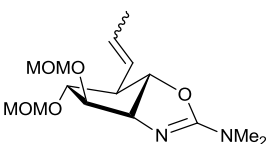
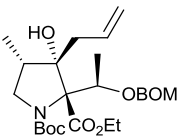
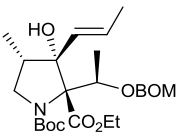
Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
1		 92%, >9:1	RhCl ₃ ·3H ₂ O (0.3 mol%), EtOH, 20 °C, 2 h	107
2		 93%, 4:1	RhCl ₃ ·3H ₂ O (0.3 mol%), EtOH, 20 °C, 2 h	107
3		 89%, 9:1	RhCl ₃ ·3H ₂ O (8 mol%), EtOH, 70 °C, 8 h	108
4		 60%, (<i>E</i>) only	RhCl ₃ ·3H ₂ O (1 mol%), PrOH, 95 °C, 10 h	109

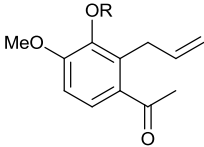
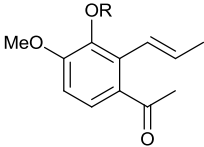
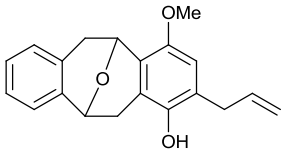
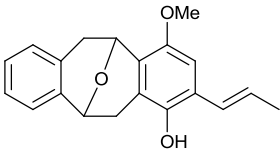
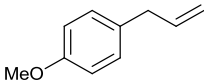
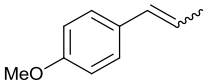
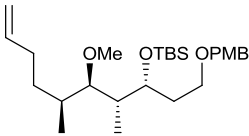
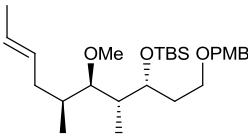
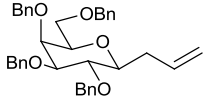
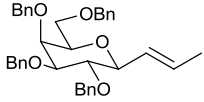
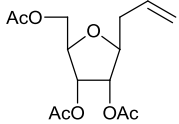
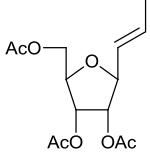
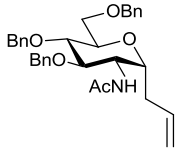
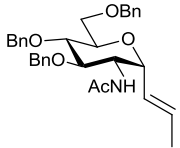
Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
5		 96%, 10:1	RhCl ₃ ·3H ₂ O (5 mol%), EtOH, 45 °C, 4 h	110
6		 97%	RhCl ₃ ·3H ₂ O (cat.), PhMe-MeOH (5:1), 70 °C, 3 h	111
7		 98%	RhCl ₃ ·3H ₂ O (cat.), EtOH, reflux	112
8	 R = MeO, Me, CO ₂ Me, NO ₂	 46 – 52%	RhCl ₃ ·nH ₂ O (cat.), EtOH, Δ, 3.5 h	113
9		 94%	RhCl ₃ ·nH ₂ O, MeOH, 70 °C, 10 h	114
10		 99%	RhCl ₃ ·3H ₂ O (2 × 5 mol%), EtOH, reflux, 2 h	115
11		 >96%	RhCl ₃ ·3H ₂ O (5 mol%), EtOH, 80 °C, 3 h	116
12		 77%	RhCl ₃ ·3H ₂ O (cat.), EtOH, reflux, 20 h	117

Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
13		 91%	RhCl ₃ ·3H ₂ O (10 mol%), K ₂ CO ₃ (18 mol%), EtOH, reflux, 2.5 h	118
14		 100%	RhCl ₃ ·nH ₂ O (3 mol%), EtOH, 70 °C, 6 h	119
15		 76%, 10:1	RhCl ₃ ·3H ₂ O (11 mol%), K ₂ CO ₃ (1.0 equiv.), EtOH, 60 °C, 2 h	120
16		 46%	RhCl ₃ ·3H ₂ O (7 mol%), EtOH, reflux, 24 h	121
17		 91%	RhCl ₃ ·3H ₂ O (cat.), EtOH, 100 °C, 30 m	122
18		 95%, 1:3	RhCl ₃ ·3H ₂ O (3 mol%), H ₂ SO ₄ , EtOH, reflux, 2 h	123

Many other transition metal-based catalysts have been utilised for the isomerisation of monosubstituted alkenes to selectively afford 1-propenyl products. Selected examples where rhodium-, ruthenium-, iridium-, palladium-, platinum- and cobalt-derived catalysts have been used for isomerisation are presented in Table 2.

Table 2. Further examples of transition metal-catalysed isomerisation of monosubstituted alkenes to their disubstituted counterparts.

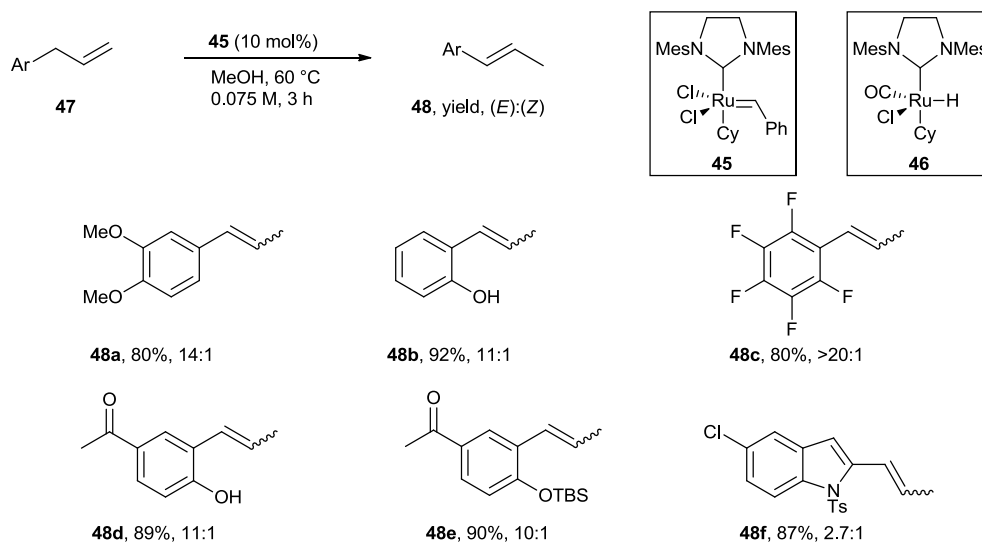
Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
1		 95%, 1:2.6	5% Rh/Al ₂ O ₃ or Rh/C (1 mol% Rh), conc. HCl _(aq) (10 equiv.), EtOH-H ₂ O (1:1), 90 °C, 24 h	124
2		 80%, 8:1	RhCl(PPh ₃) ₃ (cat.), EtOH-H ₂ O, Δ, 5 h	125
3		 83%	RuCl ₂ (PPh ₃) ₃ (2 mol%), <i>i</i> Pr ₂ NEt (8 equiv.), toluene, 130 °C, overnight	126
4		 81%, ~2:1	Grubbs' II (20 mol%), TrNH(Allyl) (2.0 equiv.), <i>i</i> Pr ₂ NEt (1.0 equiv.), toluene, reflux, 15 h	127
5		 100%, 2.3:1	Grubbs' II (5 mol%), TMSOCH=CH ₂ (10 equiv.), CH ₂ Cl ₂ , reflux, 7 h	128
6		 ~100%	Grubbs' II (5 mol%), TMSOCH=CH ₂ (10 equiv.), toluene, reflux, 15 h	129

Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
7	 <p>R = Me, <i>i</i>Pr, Bn</p>	 <p>81 – 94%</p>	PdCl ₂ (MeCN) ₂ (cat.), CH ₂ Cl ₂ , 35 °C, 72 h	130
8		 <p>86%</p>	PdCl ₂ (MeCN) ₂ (5 mol%), CH ₂ Cl ₂ , reflux, 4 h	131
9		 <p>99%, 97:3</p>	[(dppb)Pt(C ₆ F ₅)(H ₂ O)]OTf (1 mol%), CHCl ₃ , 50 °C, 12 h	132
10		 <p>98%</p>	[Ir(PCy ₃) ₃] ⁺ (2 mol%), 50:1 CH ₂ Cl ₂ :acetone	133
11		 <p>90%, (<i>E</i>) only</p>	[Ir(PPh ₂ Me) ₂ (COD)]PF ₆ (10 mol%), pre-treated with H ₂ , THF, rt, 48 h	134
12		 <p>89%, (<i>E</i>) only</p>	[Ir(PPh ₂ Me) ₂ (COD)]PF ₆ (10 mol%), pre-treated with H ₂ , THF, rt, 48 h	134
13		 <p>87%</p>	[Ir(PPh ₂ Me) ₂ (COD)]PF ₆ (10 mol%), THF, rt, 2 h	135

Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
14		 60%	$[\text{Ir}(\text{PPh}_2\text{Me})_2(\text{COD})]\text{PF}_6$ (10 mol%), THF, rt, 2 h	¹³⁵
15		 83%, 98:2	CoCl_2 (5 mol%), IMes.HCl (5 mol%), $\text{Me}_2\text{PhSiCH}_2\text{MgCl}$ (0.5 equiv.), dioxane, 50 °C, 6 h	¹³⁶
16		 80%, (<i>E</i>) only	CoCl_2 (10 mol%), IMes.HCl (10 mol%), $\text{Me}_2\text{PhSiCH}_2\text{MgCl}$ (1.0 equiv.), dioxane, 100 °C, 8 h	¹³⁶
17		 61%, (<i>E</i>) only	CoCl_2 (10 mol%), IMes.HCl (10 mol%), $\text{Me}_2\text{PhSiCH}_2\text{MgCl}$ (1.0 equiv.), dioxane, 100 °C, 8 h	¹³⁶

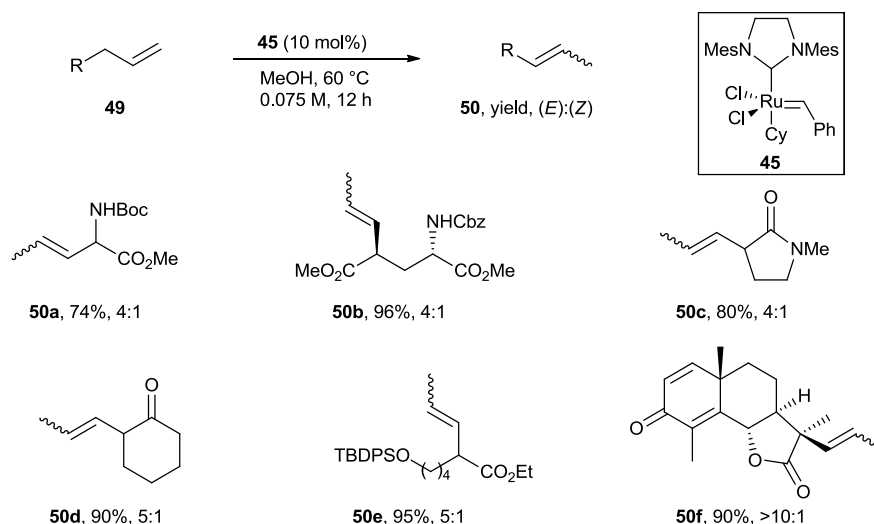
Hanessian and co-workers¹³⁷ have recently explored the reactivity of Grubbs' second generation-derived ruthenium hydride complex **46** for the isomerisation of alkenes (see Scheme 41, below). Formation of the active catalytic species **46** was achieved *in situ* upon heating a methanolic suspension of **45** and substrate to 60 °C.^{138,139} An alkene concentration of 0.075 M resulted in the occurrence of competing self-dimerization and cross-metathesis side-reactions being minimised. Initially, a range of substituted allylbenzenes **47a-e** and the 2-allylindole derivative **47f** were converted to their corresponding 1-propenyl isomers with high selectivity for their (*E*)-isomers (Scheme 41). A range of substituents in the aromatic ring were tolerated and excellent levels of conversion were observed, with isomerisation proceeding in less than three hours.

Importantly, attempts to isomerise substrates that contain coordinating functional groups, such as **47d/47e**, using conventional catalysts such as $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, $\text{RhCl}(\text{PPh}_3)_3$, or $\text{RuH}_2(\text{PPh}_3)_4$ resulted in no isomerisation occurring.



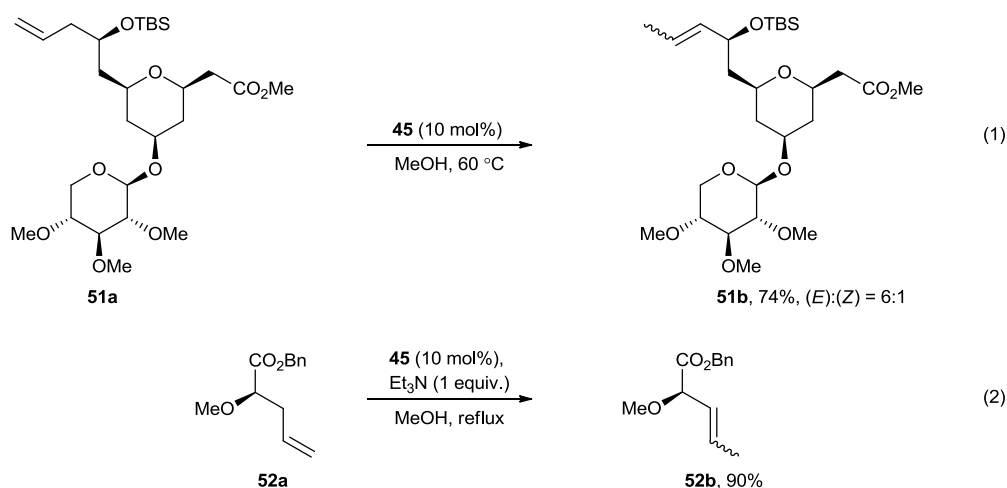
Scheme 41. Isomerisation of aryl-allyl derivatives.

The isomerisation of a variety of carbonyl containing allyl derivatives (**49**) to 1-propenyl products (**50**) was also investigated, with these substrates reacting more slowly to afford (*E*)-alkenes in high yields (Scheme 42). In all cases, no further migration of the double bond to form conjugated alkenes was observed. The isomerisation catalyst is sufficiently sensitive to steric demands in order to selectively furnish 2-alkene isomers, thus allowing facile access to α -1-propenyl carbonyl compounds that are difficult to obtain using other types of methodology.



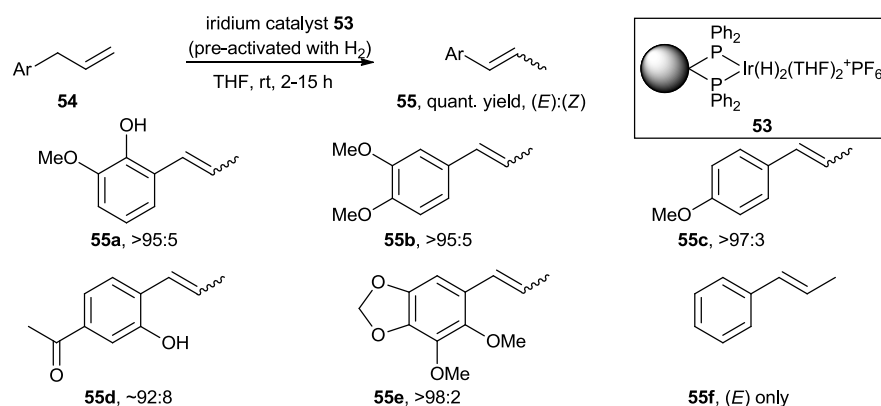
Scheme 42. Isomerisation of α -C-allyl carbonyl derivatives.

Isomerisation of terminal alkenes to their disubstituted counterparts using this catalyst system has recently been demonstrated for natural product synthesis. Willis¹⁴⁰ and co-workers isomerised an *O*-TBS protected homoallylic alcohol **51a** to its corresponding 1-propenyl derivative **51b** for use as an intermediate in the total synthesis of (–)-clavosolide D (Scheme 43, eq 1). Hanessian¹⁴¹ and co-workers have also reported isomerisation of **52a** (Scheme 43, eq 2) as part of their total synthesis of L-(+)-noviose.



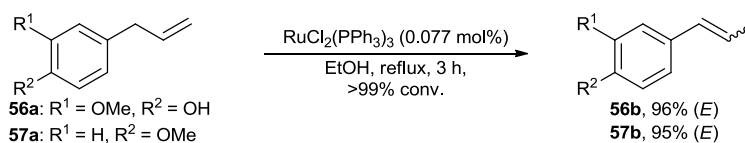
Scheme 43. Selective alkene isomerisation reactions mediated by thermally activated Grubbs' 2nd generation ruthenium carbene.

The isomerisation of a range of allylbenzene derivatives to their corresponding 1-propenyl products, using a polymer-supported iridium catalyst **53**, was reported by Ley¹⁴² and co-workers in 2002 (Scheme 44). The isomerisation reactions proceed smoothly in THF at room temperature under gentle agitation, with simple filtration and removal of solvent affording the isomerised 1-propenyl products **55a-f**. A range of substrates were isomerised with high levels of *(E)*-selectivity, although electron-deficient aromatic derivatives proved more difficult to isomerise.



Scheme 44. Isomerisation of allylbenzene derivatives using a polymer-supported iridium catalyst.

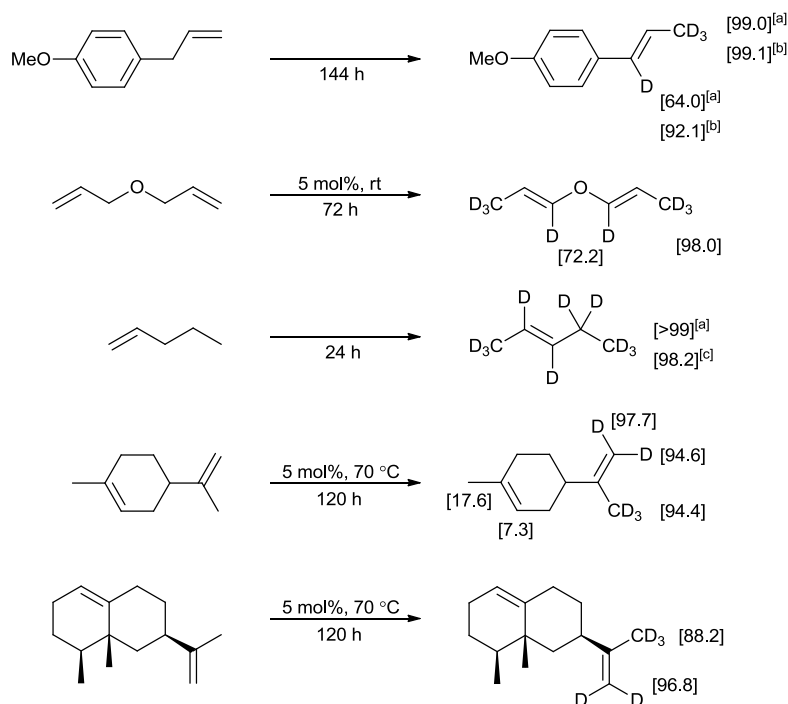
The isomerisation of aryl-allyl derivatives to form their corresponding 1-propenylbenzenes represents an “idealised” isomerisation reaction, due to the strong thermodynamic preference for the conjugated isomer and the lack of opportunity for further migration of the double bond. Numerous essential oils are rich in aryl-substituted allylbenzenes and their 1-propenyl isomers are often used as flavourings, perfumery compounds, or for the manufacture of fine chemicals.¹⁴³ An illustrative example is the conversion of estragole (**57a**, see Scheme 45 below) to anethole (**57b**), which has been carried out on an industrial scale using stoichiometric amounts of sodium or potassium hydroxide at 200 °C, resulting in an approximately 60% conversion to anethole, with a maximum (*E*):(*Z*) ratio of 82:18.^{132,144} Unfortunately, the (*Z*)-isomer is considered toxic and has an unpleasant odour and taste, with a maximum permitted level of 1% for human use, thus necessitating further purification.¹⁴⁵ A recent promising report from Jasra¹⁴⁴ described highly selective isomerisation of both eugenol (**56a**) and estragole (**57a**), catalysed by RuCl₂(PPh₃)₃. The respective (*E*)-1-propenyl isomers, (*E*)-isoeugenol (**56b**) and (*E*)-anethole (**57b**), were formed with >95% (*E*)-selectivity in almost quantitative yield (Scheme 45). Interestingly, the catalyst functioned efficiently at < 0.1 mol% loading and could be re-used up to five times in both cases, with no significant drop in either yield or stereoselectivity.



Scheme 45. Ruthenium-catalysed isomerisation of essential oil-derived allylbenzenes.

Deuterium-labelled compounds can function as useful mechanistic probes for both synthetic and biological applications, therefore a variety of methods for carrying out H–D exchange reactions at carbon centres have been devised.¹⁴⁶ As transition metal-catalysed isomerisation of alkenes usually occurs *via* C–H bond cleavage and reformation, the introduction of an external source of deuterium atoms into these isomerisation reactions can be used for the deuteration of alkene-containing substrates. However, where H–D exchange has been carried out, it is often incomplete and/or poorly regioselective. Following up on previous work¹⁴⁷ on alkene isomerisation using a novel ruthenium-based “alkene zipper” catalyst **58** (see Scheme 47), Grotjahn¹⁴⁸ has reported an effective method

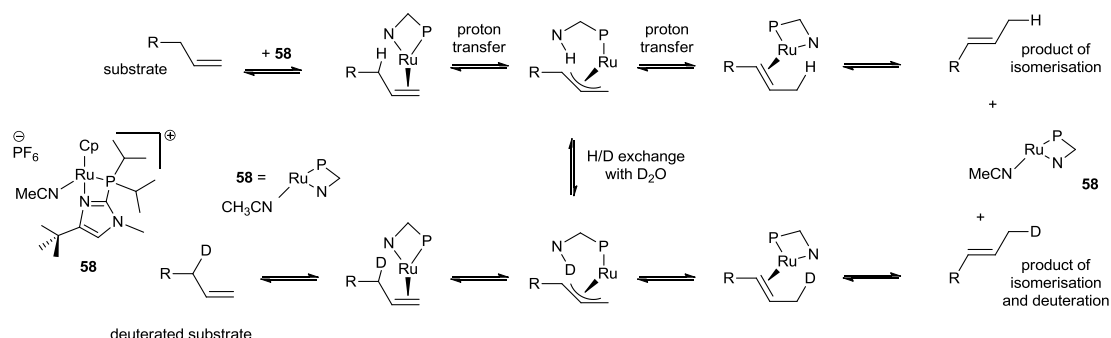
for H–D exchange of alkenes under mild conditions. Inclusion of D₂O in the acetone-*d*₆ reaction solvent resulted in efficient levels of deuteration at the alkene carbons, as well as nearby sp³ carbon centres (Scheme 46).



Scheme 46. Reactions carried out in acetone-*d*₆ with enough deuterium oxide so as to provide 20 D per exchangeable H present. The number in brackets indicates the percentage of the theoretical amount (95%) of deuterium.

[a] At rt with 2 mol% catalyst; [b] At 70 °C with 5 mol% catalyst; [c] At rt with 5 mol% catalyst.

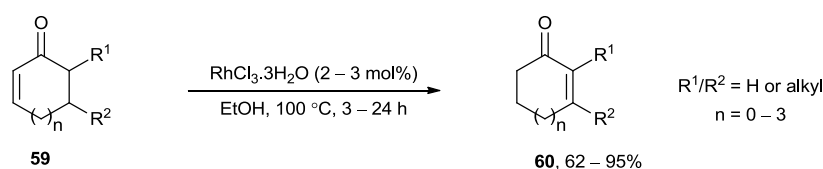
Deuteration of the substrate alkenes is thought to occur according to the mechanism outlined below (Scheme 47), where further deuterium incorporation is facilitated by H–D exchange of the protonated imidazolium ligand.



Scheme 47. Proposed mechanism of isomerisation and deuteration.

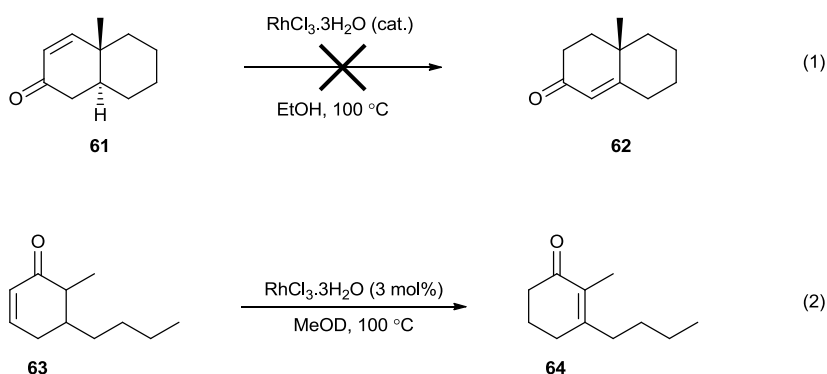
2.3.2 Isomerisation of 1,2-disubstituted alkene substrates

A landmark early report describing alkene isomerisation reactions of 1,2-disubstituted alkenes using catalytic quantities of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ was published by Grieco¹⁴⁹ in 1976. Conversion of Δ^2 -cycloalkenones **59** ($n = 0, 1, 2, 3$) to their more substituted isomers **60**, was found to occur upon treatment with 2 – 3 mol% $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ at 100 °C in absolute ethanol (Scheme 48).



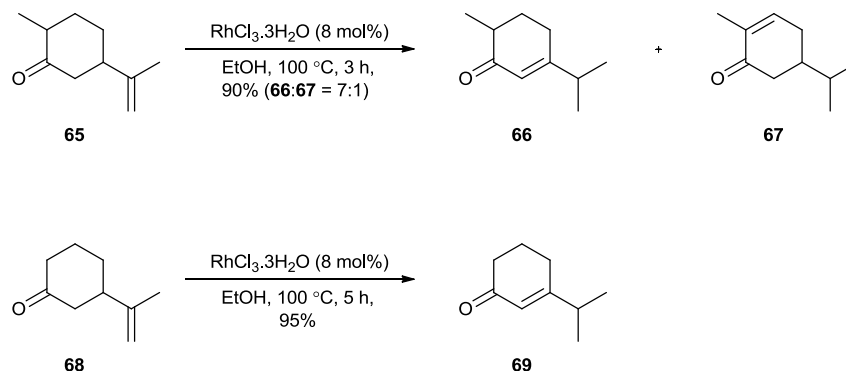
Scheme 48. Isomerisation of α,β -unsaturated cycloalkenones into their more substituted isomers, catalysed by rhodium(III) chloride trihydrate in ethanol.

The observation that $\Delta^{1,2}$ -octalone **61** could not be isomerised to the $\Delta^{4,5}$ -octalone **62** (Scheme 49, eq 1) suggested that the reaction occurs *via* rhodium-catalysed isomerisation of the double bond around the ring. Strong evidence for this hypothesis was obtained by treating cyclohexenone **63** with $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ in CH_3OD at 100 °C, with multiple ring protons of the isomerised product **64** found to have undergone deuterium exchange (Scheme 49, eq 2).



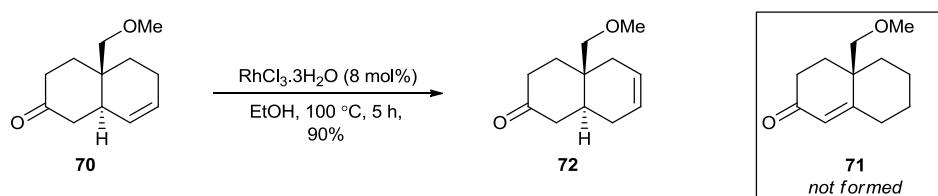
Scheme 49. Eq 1: Alkene isomerisation through a quaternary carbon centre is not possible; Eq 2: Isotopic analysis of **64** found incorporation of 0% d_{1-5} , 14% d_6 , 55% d_7 , 31% d_8 .

It was also demonstrated that the alkene bond to be isomerised could be exocyclic to a ring system, with dihydrocarvone **65** and 3-isopropenylcyclohexanone **68** being isomerised to their corresponding conjugated enones (Scheme 50), although in the former case a 7:1 mixture of the positional isomers **66** and **67** were obtained in 90% yield.



Scheme 50. Rhodium-catalysed isomerisation of 3-(2-propenyl)cyclohex-2-enones to their conjugated isomers.

The limitation of this methodology is reached when the energy of a transition state leading to an alkene isomerisation product is too high, or is *not* favoured by the catalyst/reaction conditions. For example, an attempt to isomerise γ,δ -unsaturated enone **70** to the more stable α,β -unsaturated octalone **71** resulted in the δ,ε -unsaturated isomer **72** being unexpectedly isolated in 90% yield (Scheme 51).

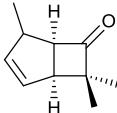
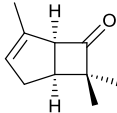
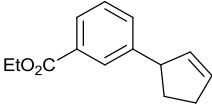
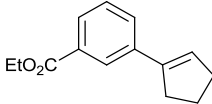
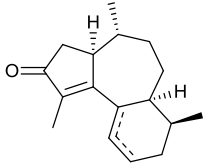
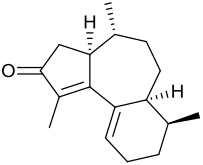
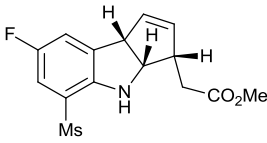
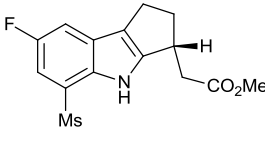


Scheme 51. Unexpected regioselectivity during rhodium-catalysed isomerisation of a γ,δ -unsaturated decalone.

Rhodium(III) chloride in its hydrated form has since been frequently used for the conversion of a wide variety of disubstituted alkene-containing substrates into their more-

substituted alkene isomers, with reactions generally being carried out in an alcoholic solvent, such as ethanol (see Table 3 for selected examples).

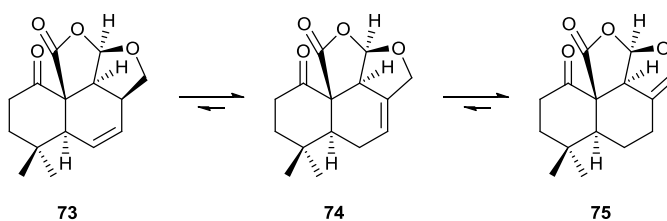
Table 3. Selected examples of RhCl₃-catalysed alkene isomerisation to the more substituted isomer.

Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
1		 35%	RhCl ₃ .nH ₂ O (cat.), EtOH-H ₂ O	150
2		 96%	RhCl ₃ .nH ₂ O (10 mol%), EtOH, 80 °C, 16 h	151
3 ^[a]		 + isomers 93 : 7	RhCl ₃ .nH ₂ O (10 mol%), EtOH, reflux	152
4	 96% ee	 100%, 55% ee	RhCl ₃ .nH ₂ O (10 mol%), EtOH, reflux, 18 h	153

[a] The isomerisation protocol was performed upon a crude elimination reaction product comprising a mixture of γ,δ - and δ,ϵ -unsaturated isomers in a ratio of 82:18, respectively.

Alkene bond migration may be used as a useful strategy for accessing late stage alkene intermediates that are less easily prepared than their isomeric counterparts. Towards this end, Jauch¹⁵⁴ employed a range of catalysts to mediate isomerisation of homoallylic ether **73** to its allylic ether **74** (Scheme 52). The use of RhCl₃.3H₂O, IrCl₃.3H₂O, RhH(CO)(PPh₃)₃ or RhCl(PPh₃)₃ resulted in isomerisation of the alkene through two C–C bonds to afford enol ether **75** as the major product. Although an intermediate trisubstituted alkene **74** was initially observed, it was shown to be further isomerised to **75** before all of

the starting material **73** was consumed. Interestingly, further experiments identified Vaska's complex, $[\text{Ir}(\text{PPh}_3)_2(\text{CO})\text{Cl}]$ as a catalyst that readily mediated the first isomerisation reaction, but was slower to catalyse the second isomerisation reaction. The use of 50 mol% of $[\text{Ir}(\text{PPh}_3)_2(\text{CO})\text{Cl}]$ in a mixed toluene:ethanol solvent (4:1, v/v) at 70 °C for six hours was found to afford the most favourable equilibrium mixture of **73/74/75** that were isolated in a ratio of 46:50:4, respectively.

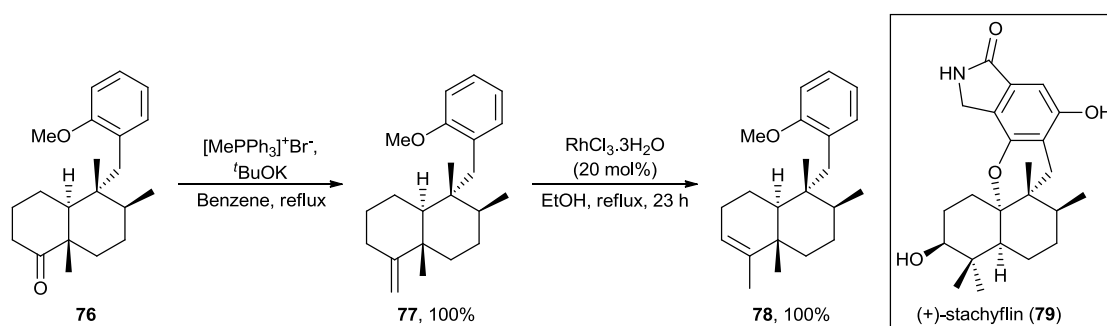


Scheme 52. Isomerisation of homoallylic ether **73** using various transition metal catalysts.

2.3.3 Isomerisation of 1,1'-disubstituted alkene substrates

Isomerisation of exocyclic methylenic alkenes to their respective endocyclic trisubstituted isomers has been widely used during synthesis and there are many different catalysts capable of achieving this transformation. Therefore, this reaction constitutes a convenient method of accessing trisubstituted alkenes that are often difficult to prepare by other routes, without recourse to multiple synthetic steps.

A common strategy employed for the synthesis of natural products involves the use of a methylene-Wittig reaction to afford an exo-methylene cyclohexane derivative followed by subsequent exo-endo double-bond isomerisation using $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$.^{155,156,157} A representative example of this approach is shown for the synthesis of the tetracyclic core of (+)-stachyflin **79** in Scheme 53.¹⁵⁸

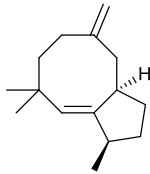
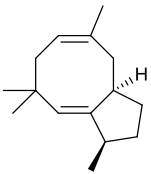
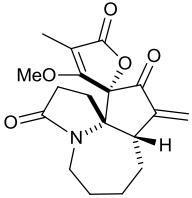
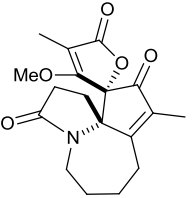
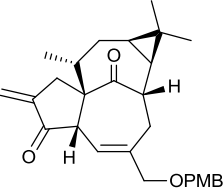
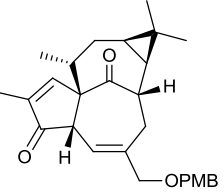
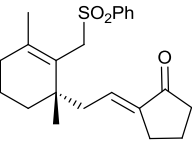
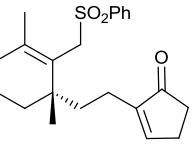
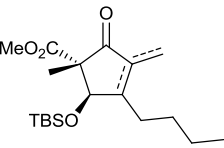
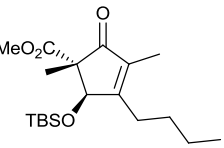
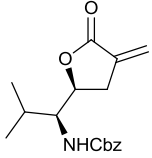
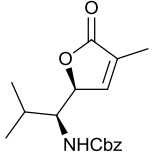
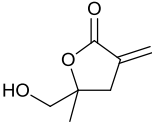
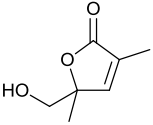


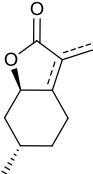
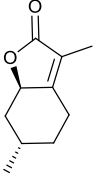
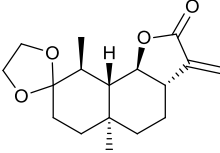
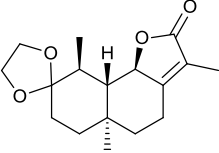
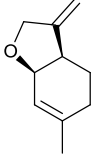
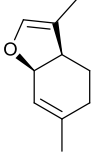
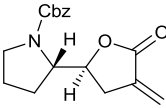
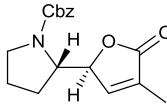
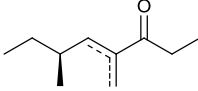
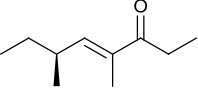
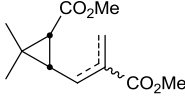
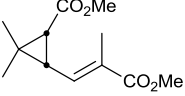
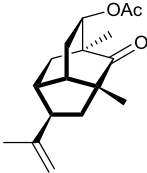
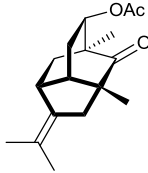
Scheme 53. Synthesis of a 1-methylcyclohexene fragment from its corresponding cyclohexanone *via* a methylene Wittig/isomerisation sequence.

Further selected examples of the wide range of rhodium-catalysed isomerisation reactions that have been used to convert substrates with exomethylenic alkene bonds to their corresponding trisubstituted alkene products are shown in Table 4.

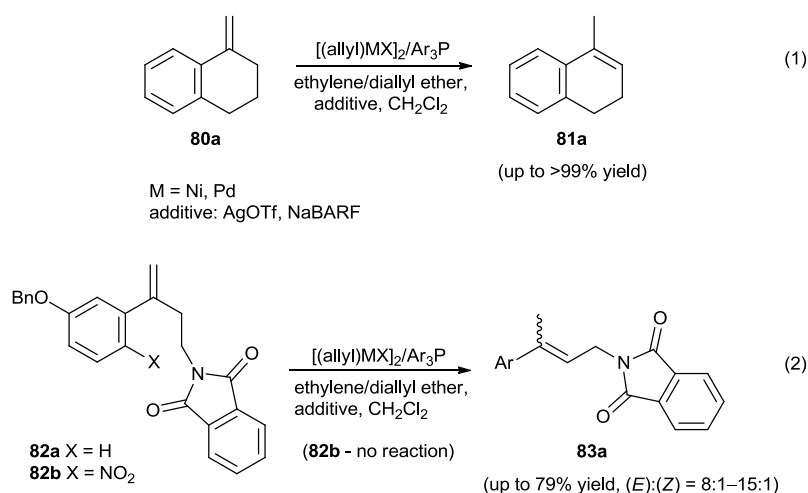
Table 4. Further examples of transition metal-catalysed isomerisation of 1,1'-disubstituted alkenes to their tri- or tetrasubstituted counterparts.

Entry	Substrate	Product, yield	Reaction conditions	Ref.
1		 67%	RhCl ₃ .3H ₂ O (cat.), EtOH-H ₂ O, 80 °C	159
2		 100%	RhCl ₃ .3H ₂ O (cat.), EtOH, reflux	160
3		 80%	RhCl ₃ .3H ₂ O (cat.), EtOH, reflux, 24 h	161
4		 100%	RhCl ₃ .nH ₂ O (5 mol%), EtOH, 75 °C, 7 h	162
5		 100%	RhCl ₃ .nH ₂ O, EtOH, 75 °C, 5 h	163

Entry	Substrate	Product, yield	Reaction conditions	Ref.
6	 <i>relative stereochemistry</i>	 50%	$\text{RhCl}_3 \cdot n\text{H}_2\text{O}$ (cat.), EtOH, 50 °C	164
7	 <i>relative stereochemistry</i>	 100%	$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (20 mol%), EtOH-H ₂ O (10:1), reflux, 30 m	165
8	 <i>relative stereochemistry</i>	 74%	$\text{RhCl}_3 \cdot n\text{H}_2\text{O}$ (30 mol%), EtOH-H ₂ O (19:1), 115 °C, 35 m	166
9		 55%	$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (6 mol%), EtOH-H ₂ O (10:1), reflux, 24 h	167
10	 1:1 exo:endo	 >73%	$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (cat.), EtOH-H ₂ O (1:1), 100 °C, 2 h	168
11	 1:1 exo:endo	 88%	$\text{RhCl}_3 \cdot n\text{H}_2\text{O}$ (10 mol%), EtOH-H ₂ O (10:1), 60 – 65 °C, 19 h	169
12		 72%	$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (1 mol%), EtOH, reflux	170

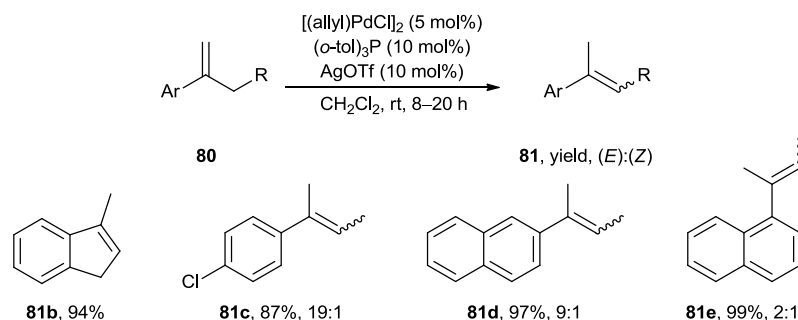
Entry	Substrate	Product, yield	Reaction conditions	Ref.
13	 <p>1.2:1 exo:endo</p>	 <p>90%</p>	<p>$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (15 mol%), EtOH, reflux</p>	171
14		 <p>56% (+ 10% acetal-deprotected material)</p>	<p>$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (15 mol%), EtOH, reflux, 3.5 h</p>	172
15		 <p>83%</p>	<p>$[\text{RhH}(\text{PPh}_3)_4]$ (cat.), toluene, reflux</p>	173
16		 <p>86%</p>	<p>$[\text{RhCl}(\text{PPh}_3)_3]$ (10 mol%), Et_3SiH (5 mol%), toluene, reflux</p>	174
17	 <p>exo:endo = 7:1</p>	 <p>97% (>99% ee)</p>	<p>$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (5 mol%), EtOH, reflux, 15 h</p>	175
18	 <p>(<i>E</i>)-endo:(<i>Z</i>)-endo:exo = 1:0.08:0.88</p>	 <p>89%</p>	<p>$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (5 mol%), EtOH, rt, 1 h, reflux, 35 m</p>	176
19		 <p>100%</p>	<p>$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (cat.), EtOH, reflux, 24 h</p>	177

In 2009, RajanBabu¹⁷⁸ reported the development of palladium(II)- and nickel(II)-catalysed stereoselective isomerisations of 1,1'-disubstituted alkenes and terminal alkenes to afford their corresponding trisubstituted and disubstituted alkenes, respectively (Scheme 54, eqs 1 and 2). Following the observation of unexpected byproducts arising from substrate isomerisation during asymmetric hydrovinylation reactions of 1,1'-disubstituted alkenes, conditions were optimised in order to maximise the yield of isomerised product. The established alkene isomerisation catalysts, $[\text{Ir}(\text{COE})\text{Cl}]_2$ and the thermally activated Grubbs' 2nd generation metathesis catalyst (**45**), were found to be ineffective for isomerisation of either **80** or **82a** under their reported conditions of operation.



Scheme 54. Isomerisation of 1-methylenetetralin (**80a**) and 1-(2-phthalimidoethyl)styrene (**82a**).

With optimised conditions in hand, $[(\text{allyl})\text{PdCl}]_2$ was used to catalyse isomerisation of a range of 2-arylbutenes **80b-e** to their corresponding trisubstituted species in excellent yields and with generally high stereoselectivities (Scheme 55).



Scheme 55. Palladium-catalysed isomerisation of 1,1'-disubstituted alkenes.

2.3.4 Isomerisation of trisubstituted and tetrasubstituted alkene substrates

Isomerisation reactions of substrates containing tri- and tetrasubstituted alkenes have been less frequently reported and normally involve formation of conjugated alkene products. Wilkinson's catalyst $[\text{RhCl}(\text{PPh}_3)_3]$ in combination with a substoichiometric quantity of triethylsilane has been used to isomerise α -alkylidenelactones and α -alkylidene cycloalkanones to their corresponding internal tetrasubstituted olefinic isomers.¹⁷⁹ Attempts to carry out rhodium-catalysed hydrosilylation of α -alkylidenebutylolactone **82** were found to result in formation of a significant amount of the isomerised alkene product **83** (Table 5, entry 1). This reaction was not observed in the absence of triethylsilane, suggesting its direct involvement in the isomerisation process. Subsequent repetition of the reaction using a catalytic quantity of triethylsilane afforded isomerised lactone **83** as the major product (entry 2).

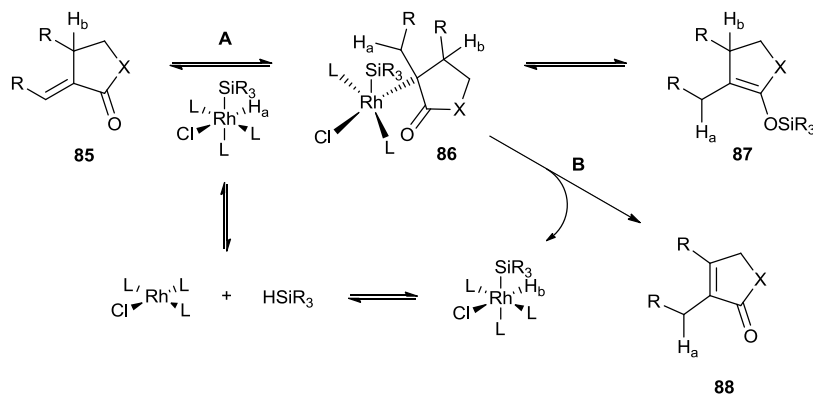
Table 5. Hydrosilylation and isomerisation of α -alkylidenebutylolactone **82**.

Reaction scheme: **82** $\xrightarrow[\text{Toluene, 110 } ^\circ\text{C}]{[\text{Rh}]/\text{Et}_3\text{SiH (cat.)}}$ **83** + **84**

Entry	Conditions	Yield/% (83:84) ^[a]
1	$\text{RhCl}(\text{PPh}_3)_3$ (0.7 mol%), Et ₃ SiH (50 equiv.)	80 (1:3)
2	$\text{RhCl}(\text{PPh}_3)_3$ (3 mol%), Et ₃ SiH (7 mol%)	93 (100:0)

[a] Isolated yield. Ratios were based on the isolated yields of each product.

The isomerisation reaction was proposed to occur *via* sequential hydrosilylation-dehydrosilylation mediated by a trialkylsilylrhodium-hydride species that is formed from oxidative addition of rhodium into the Si–H bond of triethylsilane (Scheme 56). Hydrosilylation occurs when an excess of triethylsilane is employed; however, when the concentration of triethylsilane is low, dehydrosilylation of intermediate **86** can occur *via* elimination of either H_a or H_b to afford the thermodynamically favoured trisubstituted alkene isomer.



Scheme 56. Proposed mechanism of rhodium-catalysed alkene isomerisation reactions in the presence of triethylsilane.

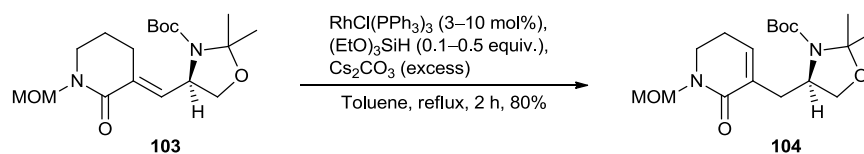
Subsequent optimisation of this isomerisation reaction established its general applicability for isomerising a range of α -alkylidenelactone and α -alkylidene cycloalkanone substrates (Table 6).

Table 6. RhCl(PPh₃)₃/Et₃SiH-catalysed isomerisation of unsaturated lactones and ketones.

Entry	Substrate	Product	Yield
1	89 : R ¹ , R ² = CH ₂	90	99
2	91 : R ¹ = R ² = Bn	92	87
3	93 : R = (CH ₂) ₂ CH ₃ , X = O	94	94
4	95 : R = 4-MeOC ₆ H ₄ , X = O	96	80
7	97	98	89
8	99 : R ¹ = R ² = Bn, R ³ = Me	100	94
9	101 : R ¹ , R ² = CH ₂ , R ³ = Me	102	94

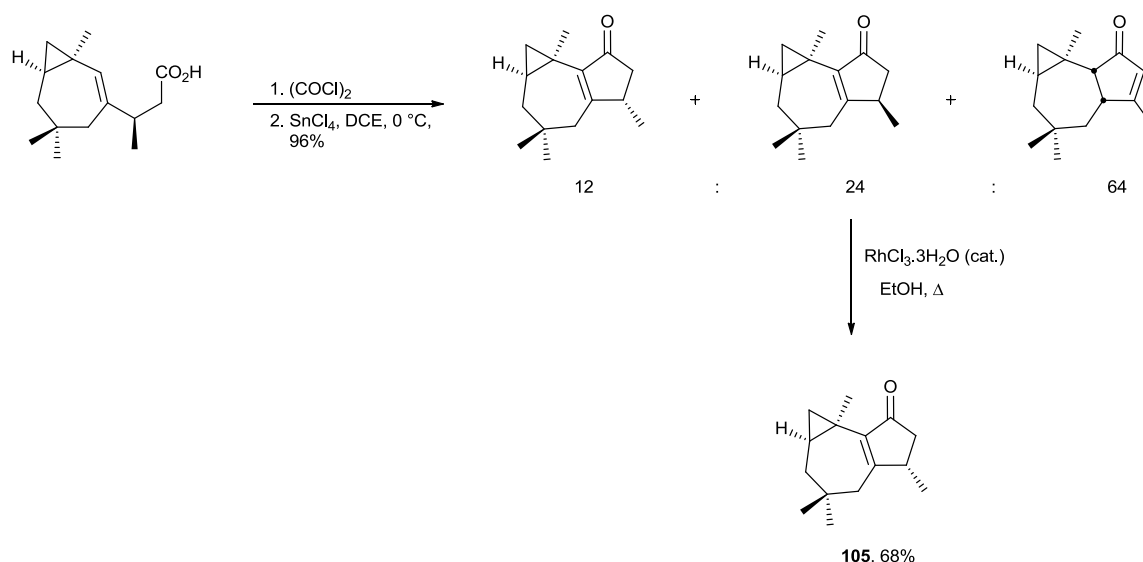
[a] Isolated yield.

Pyridone **103** was prepared via an aldol condensation reaction and isomerised into its trisubstituted derivative **104** in 80% yield *via* treatment with $\text{RhCl}(\text{PPh}_3)_3$, triethoxysilane and excess Cs_2CO_3 in refluxing toluene (Scheme 57).¹⁸⁰



Scheme 57. Rhodium-catalysed isomerisation of an aldol condensation product.

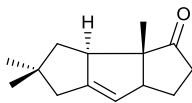
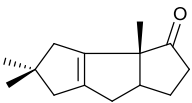
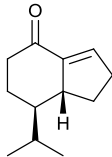
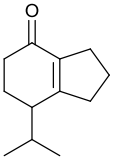
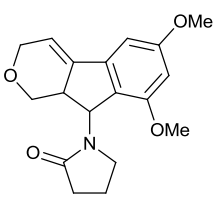
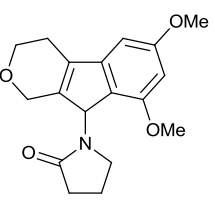
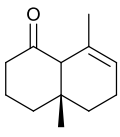
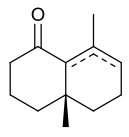
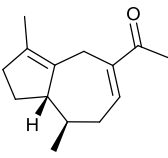
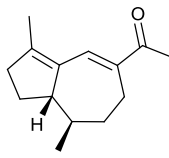
Alkene isomerisation reactions have also been used to increase the proportion of a positional isomer formed in a non-selective alkene bond forming reaction prior to chromatographic purification. For example, Paquette¹⁸¹ reported the use of rhodium(III) chloride trihydrate to equilibrate a mixture of diastereomeric alkenes obtained from an intramolecular Friedel-Crafts acylation reaction to afford a tetrasubstituted alkene **105** (Scheme 58).



Scheme 58. Equilibration of an isomeric mixture of alkenes using rhodium(III) chloride trihydrate.

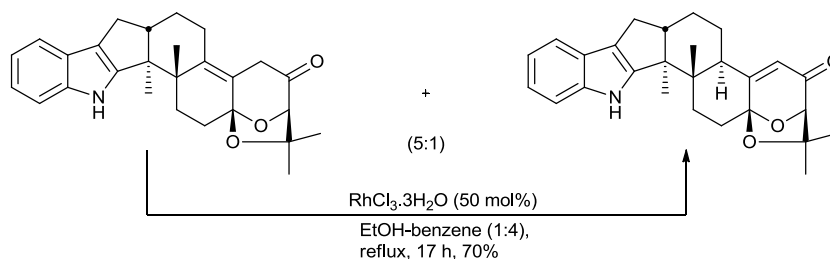
Rhodium(III) chloride trihydrate has also been utilised for the isomerisation of a range of trisubstituted alkenes to afford their corresponding di-, tri- or tetrasubstituted isomers, with selected examples shown below in Table 7.

Table 7. Further examples of rhodium-catalysed isomerisation reactions of trisubstituted alkene substrates.

Entry	Substrate	Product, yield	Reaction conditions	Ref.
1		 (yield not stated)	RhCl ₃ ·3H ₂ O (cat.), EtOH, reflux, 30 m	182
2		 50%	RhCl ₃ ·3H ₂ O (7 mol%), EtOH-H ₂ O (10:1), reflux, 3.5 d	183
3		 83%	RhCl ₃ ·3H ₂ O (10 mol%), EtOH, 100 °C, 16 h	184
4		 99%, α,β:β,γ = 2:1	RhCl ₃ ·3H ₂ O (10 mol%), benzene-EtOH (4:1), reflux, 28 h	185
5		 55%	RhCl ₃ ·3H ₂ O (23 mol%), EtOH, reflux, 24 h	186

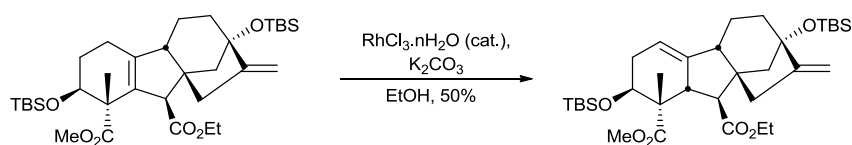
Entry	Substrate	Product, yield	Reaction conditions	Ref.
6		 3 : 2 90%	RhCl ₃ ·3H ₂ O (8 mol%), EtOH, reflux, 3 h	187
7		 53%	RhCl ₃ ·3H ₂ O (cat.), EtOH, reflux, 24 h	188

Positional isomerisation reactions of tetrasubstituted alkenes have been reported less frequently, with protocols normally involving formation of conjugated alkenes, or relief of steric strain. For example, a 5:1 mixture of β,γ - and α,β -unsaturated polycyclic enones was treated with rhodium(III) chloride trihydrate to afford the conjugated enone isomer in 70% isolated yield, during Smith's 1992 synthesis of (+)-paspalicine (Scheme 59).¹⁸⁹



Scheme 59. Isomerisation of a tetrasubstituted alkene during the synthesis of (+)-paspalicine.

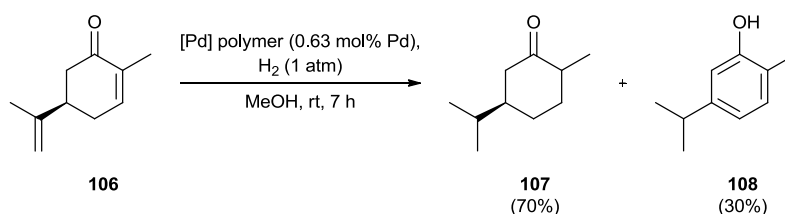
A synthesis of giberellins (+)-GA₁ and (+)-GA₃, reported in 1995 by De Clereq,¹⁹⁰ also features rhodium-catalysed isomerisation of a tetrasubstituted alkene (Scheme 60), with the isomerisation equilibria being driven by relief of transannular strain.



Scheme 60. Isomerisation of a tetrasubstituted alkene during the synthesis of giberellins.

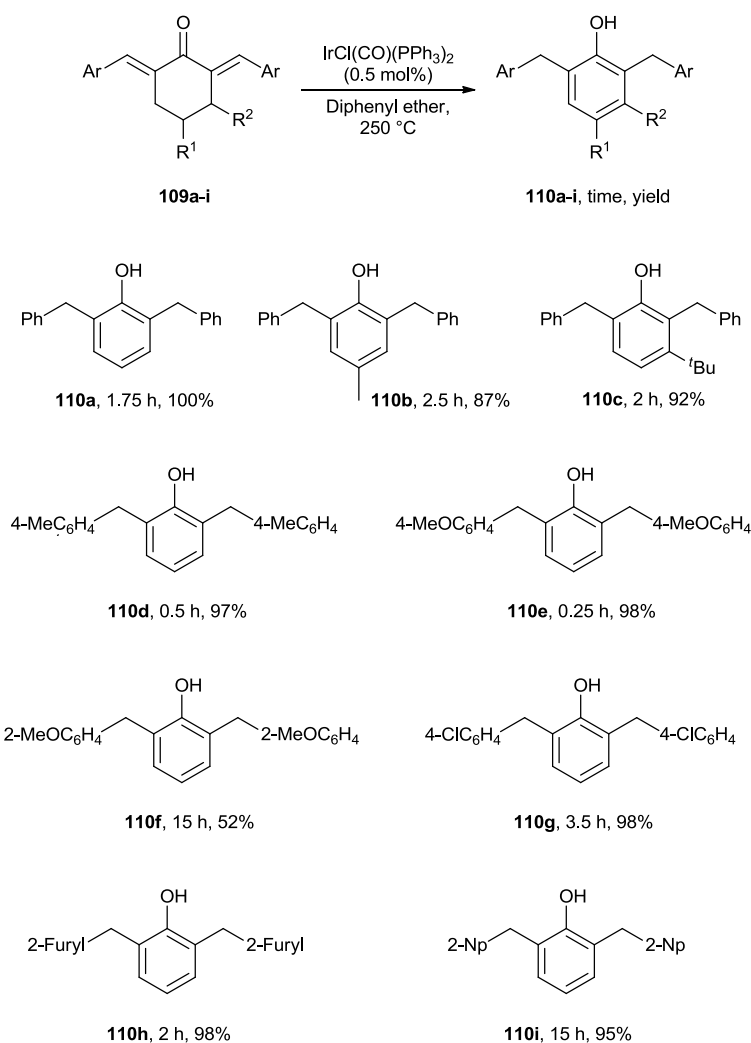
2.4 Isoaromatisation

The process of isoaromatisation¹⁹¹ involves the net movement of unsaturation within a molecular framework that results in formation of an aromatic system. This can occur, for example, in a cyclohexadienyl ring, where migration of a third exocyclic double bond occurs to complete an aromatic sextet. Most commonly, migration of a single alkene bond into a cyclohexenone system is followed by an irreversible keto-enol tautomerisation to afford a phenolic product. For example, attempts to hydrogenate carvone often result in contamination of the saturated ketone product by variable amounts of the isomeric phenol formed from competing isomerisation reactions.^{192,193} For example, hydrogenation of (–)-carvone (**106**) using a polymer-supported palladium catalyst resulted in 70% hydrogenation to carvomenthone (**107**), with the remaining 30% of starting material being isomerised to form carvacrol (**108**, Scheme 61).¹⁹⁴ This reflects the ease with which palladium-hydride species can induce alkene isomerisation as well as the strong thermodynamic preference for the formation of aromatic rings.



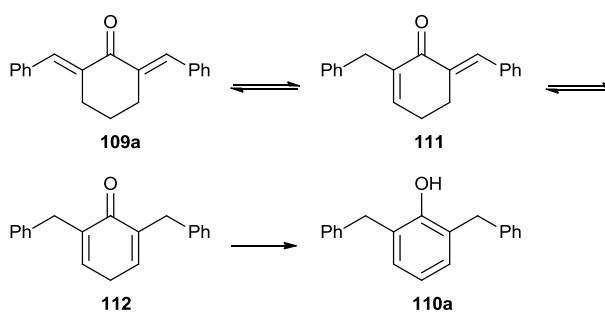
Scheme 61. Hydrogenation of (–)-carvone **106**, accompanied by isoaromatisation.

In 1974, Blum and co-workers¹⁹⁵ reported some preliminary results concerning the ability of various homogeneous transition metal catalysts (i.e., IrCl(CO)(PPh₃)₂, RhCl(PPh₃)₃ and RuCl₂(PPh₃)₃) to isomerise diarylidencyclohexanones to their corresponding phenols at 250 °C. Good yields of substituted phenols were obtained in most cases (Scheme 62), although the presence of an *ortho*-methoxy group led to a reduced yield of its corresponding phenol (52%), whilst the presence of an *ortho*-chloro substituent effectively blocked the isomerisation pathway.¹⁹⁶



Scheme 62. Isoaromatisation of bis(arylmethylene)cyclohexanones catalysed by $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$.

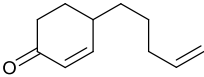
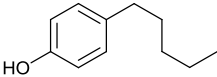
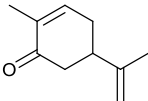
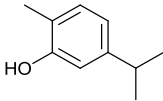
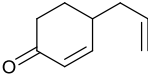
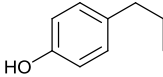
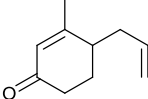
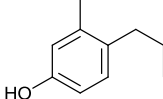
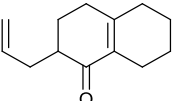
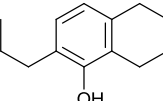
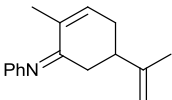
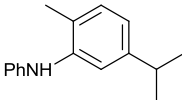
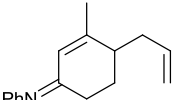
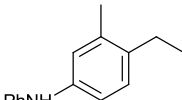
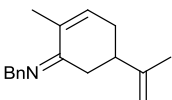
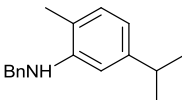
Monitoring the iridium-catalysed reaction of 2,6-dibenzylidenecyclohexanone (**109a**) by ^1H NMR spectroscopy revealed that its conversion to a phenol occurs by sequential exo-endo isomerisation of the arylidene double bonds to form intermediates **111** and **112**, followed by thermal tautomerisation to afford 2,6-dibenzylphenol **110a** (Scheme 63).



Scheme 63. Intermediates formed during the iridium-catalysed isoaromatisation of 2,6-dibenzylidenecyclohexanone **109a**, as determined by ^1H NMR spectroscopy.

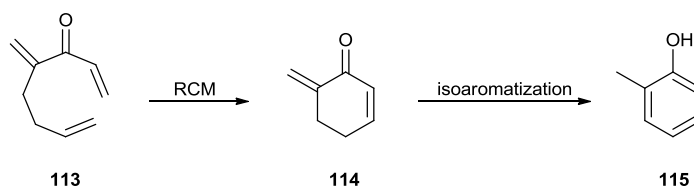
In 1978, Grieco¹⁹⁷ reported isoaromatisation of cyclohexenones and their corresponding oximes under relatively mild conditions, catalysed by treatment with 10 – 15 mol% $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, to afford their corresponding substituted phenols and anilines in good yield (Table 8).

Table 8. Formation of substituted phenols and anilines *via* RhCl_3 -catalysed isoaromatisation.

Entry ^[a]	Substrate	Product	Yield
1			62
2			78
3			60
4			65
5			69
6			50
7			51
8			47

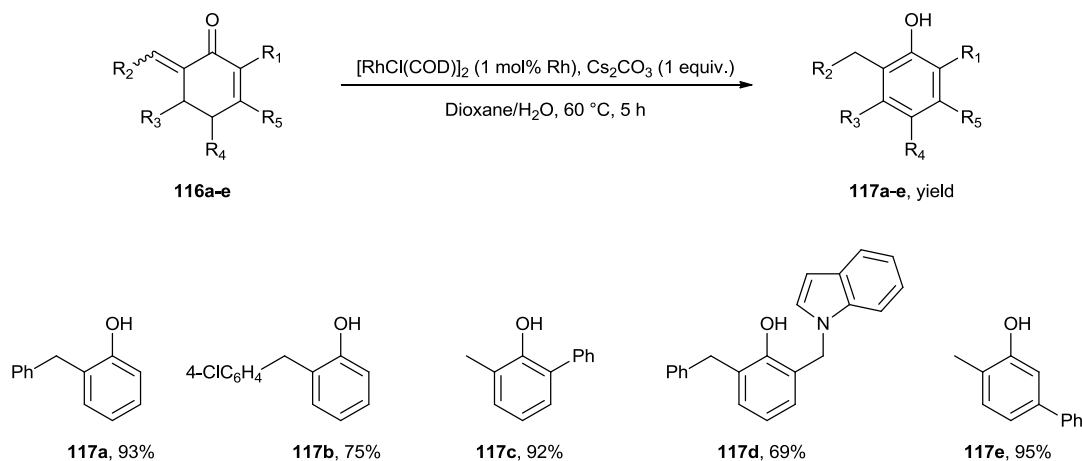
[a] Reagents and conditions, entries 1 – 5: $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (10 mol%), EtOH, 100 °C, 8 h; entries 6 – 8: $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ (15 mol%), K_2CO_3 (1.4 equiv.), EtOH, 100 °C, 30 h.

More recently, substituted 2-cyclohexenones featuring a second exocyclic double bond have been constructed using ring-closing metathesis reactions, followed by isoaromatisation to afford the corresponding phenol (Scheme 64).¹⁹⁸



Scheme 64. The RCM-isoaromatisation strategy for the synthesis of substituted phenols.

A range of conditions previously used for the isomerisation of alkene bonds were screened, using model substrate **114**, which resulted in $[\text{RhCl}(\text{COD})]_2$ and caesium carbonate (1 equiv.) in aqueous dioxane (60 °C) being identified as the catalyst system of choice. These optimised reaction conditions were applied for the isoaromatisation of several highly substituted 6-methylidene-2-cyclohexenones, affording the corresponding phenols in good to excellent yields (Scheme 65).

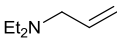
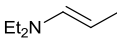
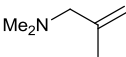
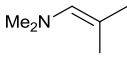
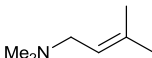
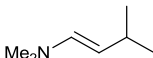
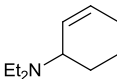
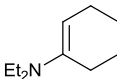
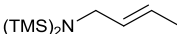
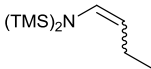
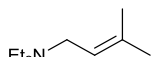
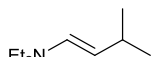


Scheme 65. Synthesis of substituted phenols by isoaromatisation.

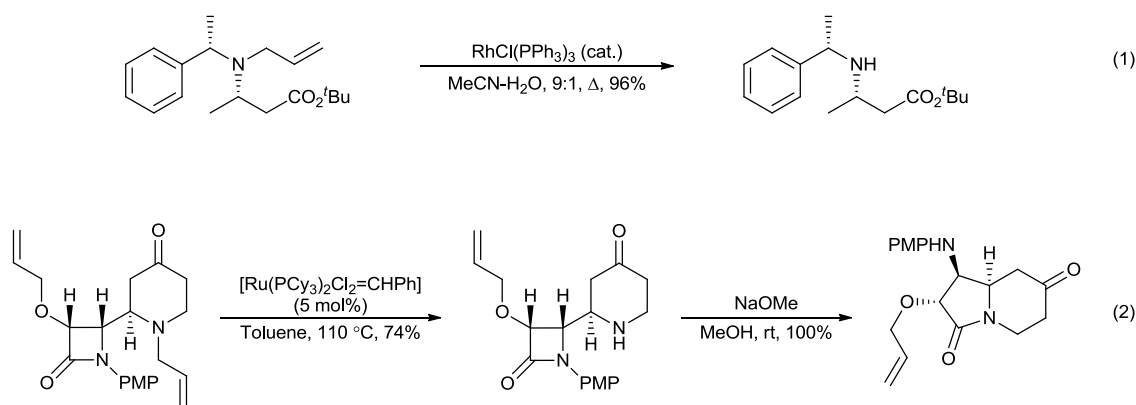
2.5 *N*-Allyl isomerisation

The isomerisation of *N*-allyl amines to afford enamines or amino groups is one of the most synthetically important double-bond migration reactions catalysed by transition-metal complexes, whose synthetic applications have been extensively reviewed.¹⁹⁹ Briefly, the resultant (*E*)-enamine products can be isolated as potentially useful synthetic intermediates in good yield using a range of different transition metal catalysts (see Table 9 for selected examples).

Table 9. Transition metal-catalysed isomerisation of *N*-allyl amines to their corresponding enamines.

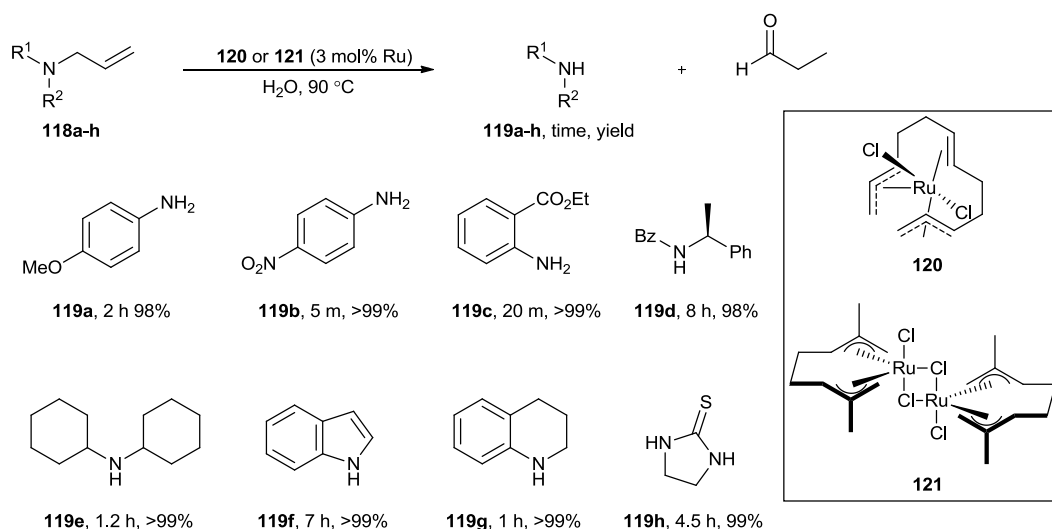
$ \begin{array}{ccc} \begin{array}{c} \text{R}^2 \quad \text{R}^4 \\ \diagup \quad \diagdown \\ (\text{R}^1)_2\text{N}-\text{C}=\text{C}-\text{R}^5 \\ \diagdown \quad \diagup \\ \text{R}^3 \end{array} & \xrightarrow[\text{solvent, temp., time}]{[\text{M}] \text{ (cat.)}} & \begin{array}{c} \text{R}^2 \quad \text{R}^4 \\ \diagup \quad \diagdown \\ (\text{R}^1)_2\text{N}-\text{C}=\text{C}-\text{R}^5 \\ \diagdown \quad \diagup \\ \text{R}^3 \end{array} \end{array} $				
Entry	Substrate	Product, yield, (<i>E</i>):(<i>Z</i>)	Reaction conditions	Ref.
1		 100%, (<i>E</i>) only	<i>trans</i> -Mo(N ₂) ₂ (dppe) ₂ (10 mol%), toluene, 110 °C, 2 h	200
2		 97%	[Rh(BINAP)(COD)]ClO ₄ (1 mol%), H ₂ , THF- <i>d</i> ₈ , 60 °C, 23 h	201
3		 100%, (<i>E</i>) only	[Rh(BINAP)(COD)]ClO ₄ (1 mol%), H ₂ , THF- <i>d</i> ₈ , 60 °C, 23 h	198
4		 89%	[Rh(BINAP)(COD)]ClO ₄ (1 mol%), H ₂ , THF- <i>d</i> ₈ , 60 °C, 23 h	198
5		 84%, 30:70	[Fe(CO) ₅] (10 mol%) + <i>hν</i> , hexane, 20 °C, 15 h	202
6		 100%, (<i>E</i>) only	[CoH(N ₂)(PPh ₃) ₃] (1 mol%), THF, 80 °C, 15 h	203

Transition metal-catalysed isomerisation of *N*-allyl species has also been applied as a strategy for selective *N*-deprotection of *N*-allylic amines, amides and lactams. For example, treatment of *N*-allyl tertiary amines with Wilkinson's catalyst has been reported by Davies and co-workers²⁰⁴ for the synthesis of enantiopure β -amino esters (Scheme 66, eq 1). Alternatively, a highly chemoselective *N*-deallylation reaction in the presence of an *O*-allyl ether, mediated by Grubbs' ruthenium carbene has been reported by Alcaide²⁰⁵ for the synthesis of enantiopure indolizidines (Scheme 66, eq 2).



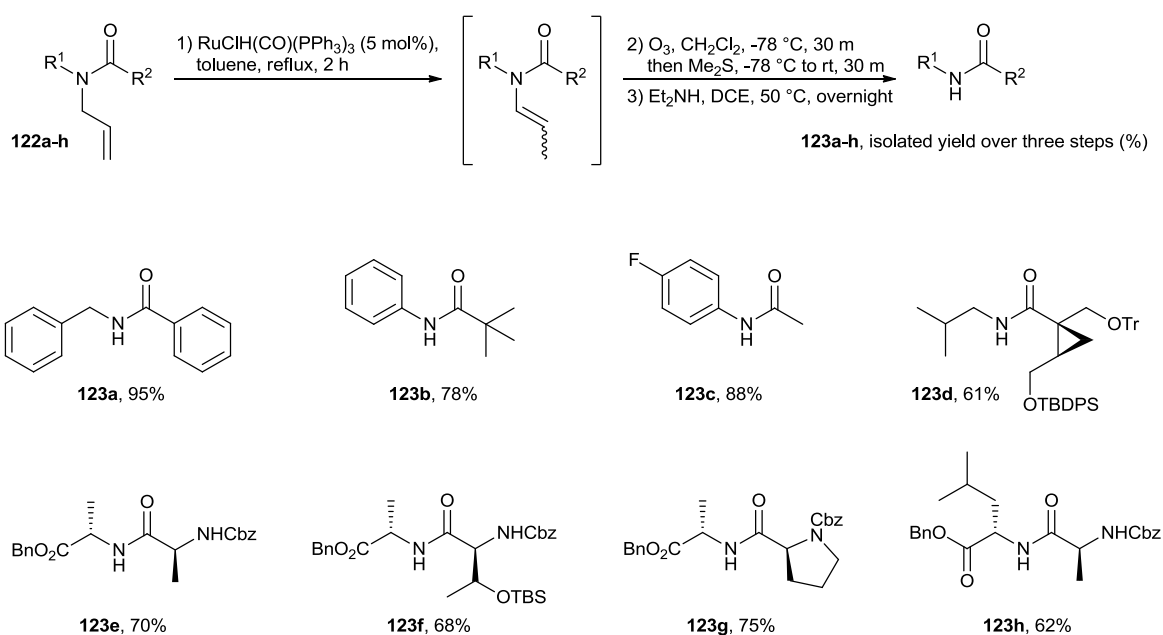
Scheme 66. Transition metal-catalysed methods of chemoselective *N*-allylamine deprotection.

Although the chemoselectivity displayed by Grubbs' ruthenium carbene complex is impressive, this catalyst is known to undergo competing metathesis reactions when applied to the isomerisation of *N,N*-diallyl species.²⁰⁶ However, some ruthenium complexes have been developed for exhaustive deallylations of both *N,N*-diallylaniline and *N,N*-diallyl-4-nitroaniline, as well as for a large range of *N*-allylamides, heterocycles, primary and secondary amines (Scheme 67).²⁰⁷



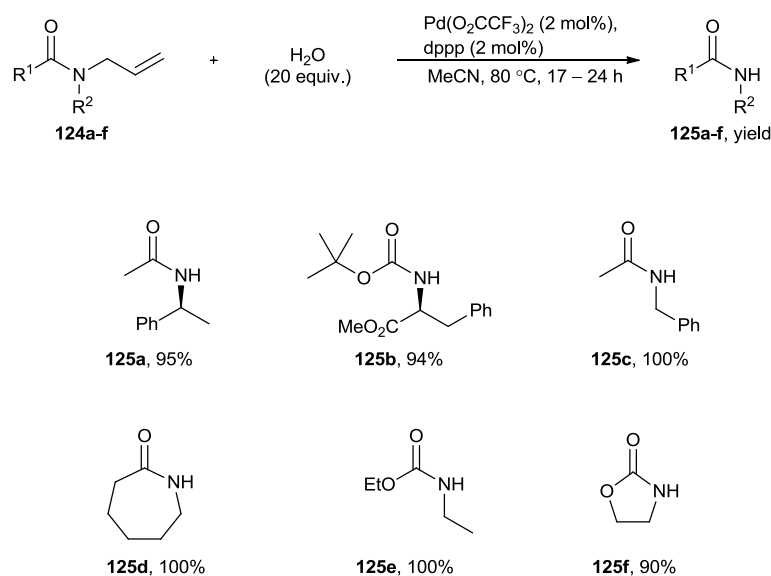
Scheme 67. Tandem ruthenium-catalysed isomerisation-hydrolysis protocol for deprotection of *N*-allyl compounds.

A one-pot isomerisation-oxidative deprotection protocol for *N*-allylamides was reported by Shuto and co-workers,²⁰⁸ using the well-known alkene isomerisation catalyst $[\text{RuCl}(\text{CO})\text{H}(\text{PPh}_3)_3]$ for the isomerisation step. A range of amides were efficiently deprotected in good to excellent overall yields, with the procedure being applied to the synthesis of various dipeptides (Scheme 68).



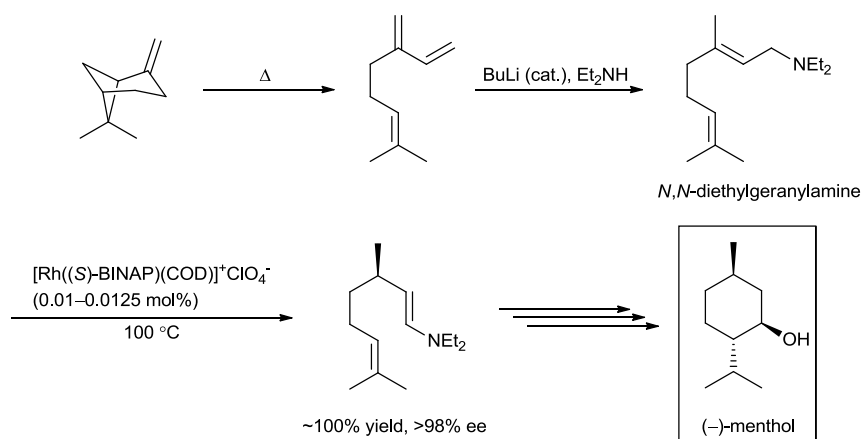
Scheme 68. One-pot ruthenium-catalysed isomerisation-oxidative deprotection of *N*-allylamides.

Alternatively, *N*-allylamides can be deprotected upon heating with palladium(II) trifluoroacetate in the presence of a diphosphine ligand and water, as reported by Tokunaga and co-workers (Scheme 69).²⁰⁹



Scheme 69. Palladium-mediated hydrolytic cleavage of *N*-allylamides.

Various asymmetric isomerisation reactions of prochiral allylic amines have been reported, with rhodium being the transition-metal most often employed for this purpose,²¹⁰ such as the famous asymmetric isomerisation of *N,N*-diethylgeranylamine that is used as a key step in the Takasago synthesis of (–)-menthol (Scheme 70).^{198,211}



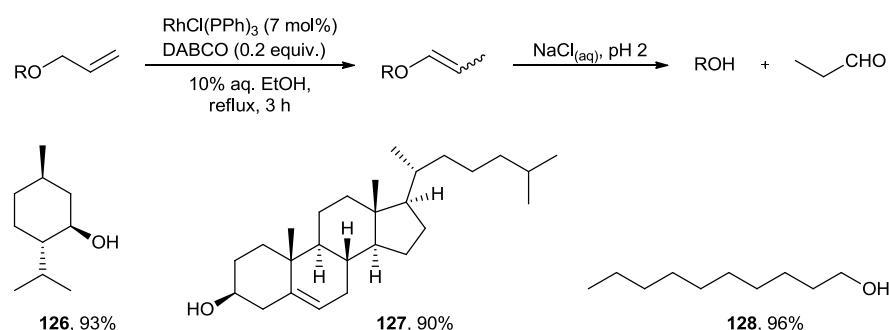
Scheme 70. The Takasago process for the asymmetric synthesis of (–)-menthol.

2.6 Isomerisation of *O*-allyl and *S*-allyl compounds

2.6.1 *O*-Allyl ethers

In 2007, Kuźnik and Krompiec published a short but comprehensive review of alkene bond migration in *O*-allyl systems, catalysed by transition metal complexes.²¹² Examples of isomerisation reactions of allylic ethers, allyl silyl ethers, allylic carboxylates and allylic acetals, tandem metathesis and Claisen rearrangement reactions involving isomerisation of *O*-allylic substrates, were also described. This review also includes a thorough discussion of various mechanistic and stereoselectivity models that have been developed to explain the outcome of these isomerisation reactions.

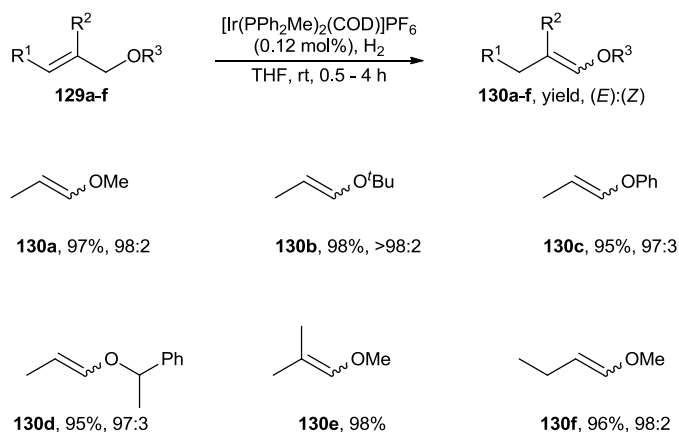
In 1973, Corey²¹³ reported the first transition-metal catalysed isomerisation of *O*-allyl ethers, followed by hydrolysis with dilute aqueous hydrochloric acid, as a chemoselective method for their deprotection (Scheme 71). The isomerisation reaction was carried out by heating the allyl ether with Wilkinson's catalyst $\text{RhCl}(\text{PPh}_3)_3$ in aqueous ethanol, in the presence of DABCO to prevent catalyst poisoning due to aldehyde formation. Under these reaction conditions other alcohol protecting groups, such as benzyl ethers, aryl ethers, alkyl ethers and esters, remain unaffected. Previous methods for the deprotection of allyl ethers involved the use of strong acids, oxidation with SeO_2 ,²¹⁴ or treatment with strong base²¹⁵ to form enol ethers which were subsequently hydrolysed or oxidised.



Scheme 71. Deprotection of allyl ethers *via* isomerisation to their corresponding enol ethers.

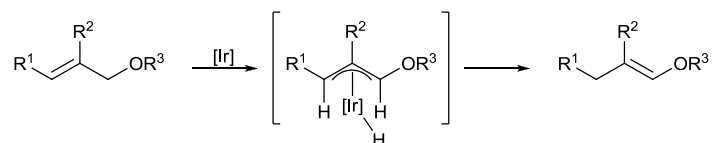
An early example of stereoselective allyl ether isomerisation with respect to alkene geometry was reported by Felkin,²¹⁶ in 1978. Hydrogen activation of the cationic iridium complex $[\text{Ir}(\text{PPh}_2\text{Me})_2(\text{COD})]\text{PF}_6$ resulted in a catalyst which was found to selectively

isomerise various *O*-allyl ethers to (*E*)-1-propenyl ethers (Scheme 72). Particularly impressive features of this reaction are the excellent (*E*):(*Z*) ratios of the products obtained (>30:1), the low catalyst loading required, the extremely mild conditions and short reaction times. However, it appears to be limited to primary allylic ether substrates, since attempted isomerisation of secondary allylic ethers under the same conditions resulted in no reaction, even at 65 °C.



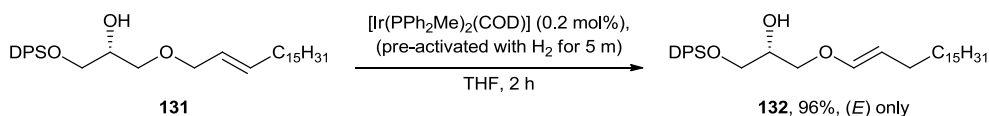
Scheme 72. Isomerisation of allyl ethers to enol ethers catalysed by $[\text{Ir}(\text{PPh}_2\text{Me})_2(\text{COD})]\text{PF}_6$ at room temperature in THF.

Isomerisation of [1,1-²H₂]allyl methyl ether (*cf.* **129a**) was shown to afford the (*E*)-1-propenyl methyl ether (*cf.* **130a**) with deuterium incorporated at C₃ and C₁ of the allyl group, but not at C₂. This strongly implies that isomerisation occurs *via* formation of a π -allyliridium hydride intermediate, as shown in Scheme 73. It appears that there is sufficient steric demand to ensure that the catalyst can only form a π -allyl complex with a *syn* configuration, whose hydrogen atoms occupy ‘*endo*’ positions. Such an intermediate can only lead to formation of (*E*)-enol ethers and could also only be formed from primary allylic ethers.



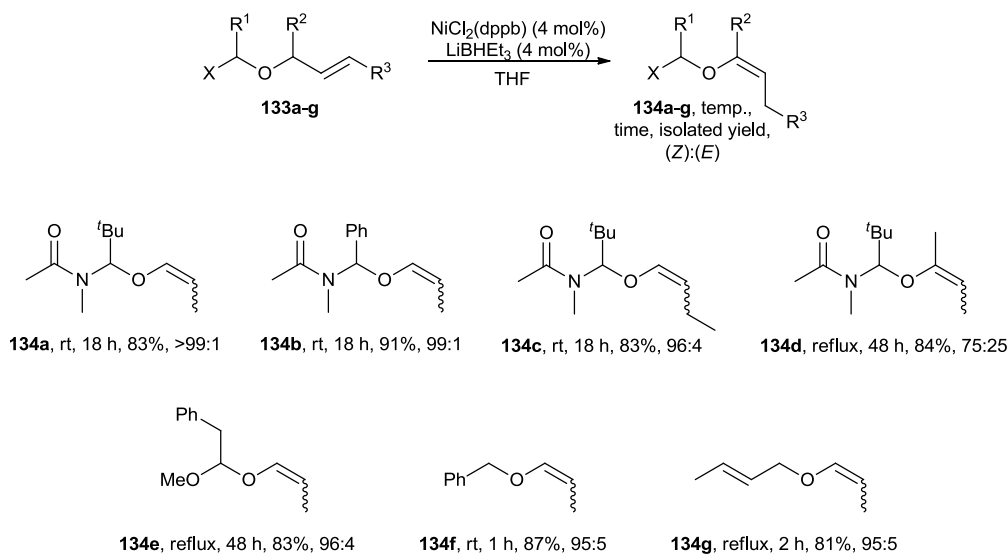
Scheme 73. Mechanism of allyl ether isomerisation *via* formation of a π -allyliridium hydride species.

The reaction has often been utilised for the removal of *O*-allyl protecting groups, *via* isomerisation followed by acid-,²¹⁷ NIS-,²¹⁸ or mercury(II)-mediated^{219,220} hydrolytic cleavage of the resultant 1-propenyl ethers. For example, this procedure was recently used by Bittman²²¹ in order to isomerise *O*-allyl ether **131** during the synthesis of an unnatural plasmalogen analogue, affording vinyl ether **132** with exclusive (*E*)-selectivity (Scheme 74).



Scheme 74. Highly (*E*)-selective iridium-catalysed isomerisation of an allyl ether during total synthesis.

A complimentary, highly (*Z*)-selective isomerisation procedure for allylic acetals and ethers was reported by Frauenrath, in 1998.²²² Treatment of a range of substrates with 4 mol% $\text{NiCl}_2(\text{dppb})$, activated with an equimolar quantity of LiBHEt_3 led to formation of the corresponding (*Z*)-1-propenyl species with excellent stereocontrol, with the exception of 3-buten-2-yl ether **133d** which afforded a 75:25 mixture of (*Z*)- and (*E*)-isomers, respectively (Scheme 75).

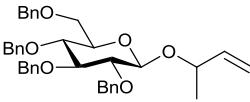
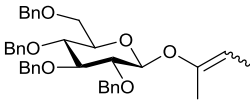
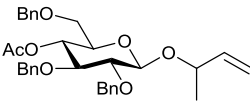
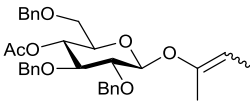
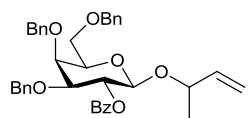
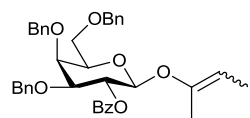
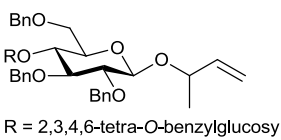
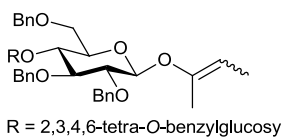
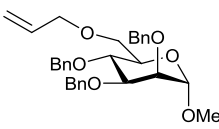
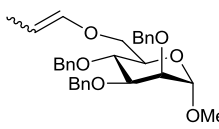
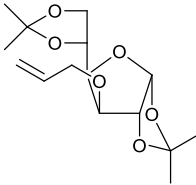
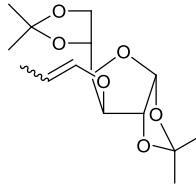
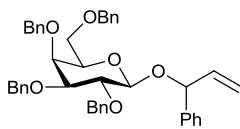
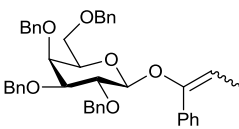


Scheme 75. $\text{NiCl}_2\text{dppb}/\text{LiBHEt}_3$ -catalysed isomerisation of acyclic allyl acetals and allyl ethers.

The original method introduced by Corey²¹³ has since been used extensively for the selective deprotection of *O*-allyl ethers, particularly for applications in carbohydrate chemistry,^{223,224,225,226,227} and for the preparation of 1-propenyl ethers as substrates for Diels-Alder reactions.²²⁸ A recent report from Golding described the direct removal of a phenolic allyl ether using Corey's conditions, without the need for an acidic hydrolytic work-up step.²²⁹ Other transition metals, such as palladium,²³⁰ iridium²³¹ and ruthenium²³² have also been used to carry out the isomerisation of allyl ethers, prior to hydrolytic cleavage of the resulting 1-propenyl ethers.

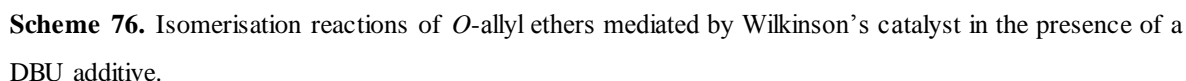
In 1996, Boons²³³ reported a modification of Corey's protocol²¹³ for the isomerisation of *O*-allyl glycosides to form novel glycoside donors. Pre-treatment of Wilkinson's catalyst with 1.5 equivalents of *n*-BuLi in THF afforded a catalyst which efficiently isomerised a range of allylic glycosides to their vinylic counterparts, without the requirement for a DABCO additive (Table 10). The reduction of allyl ethers to *n*-propyl ethers, which had previously been found to occur^{234,235,236} using Wilkinson's catalyst *via* transfer of hydrogen from the alcohol solvent was also avoided. The active catalyst is likely to be RhH(PPh₃)₃, formed *via* replacement of the chloride ligand with a butyl group that then undergoes β-hydrogen elimination. Independent preparation of this complex revealed that it possessed almost identical activity to that formed *in situ* from *n*-BuLi and Wilkinson's catalyst.

Table 10. Isomerisation of allyl ethers and glycosides using modified Wilkinson catalyst.

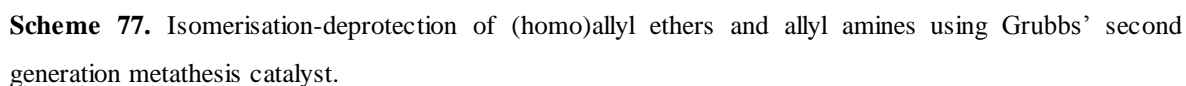
$ \begin{array}{c} \text{RhCl(PPh}_3)_3 \\ (5 - 10 \text{ mol}\%) \\ \downarrow \\ \text{THF} \\ \downarrow \\ \text{R-allyl glycoside } \mathbf{135} \xrightarrow[\text{THF, reflux, 10 m}]{\text{"active catalyst", } n\text{-BuLi (1.5 equiv)}} \text{R-allyl glycoside } \mathbf{136} \\ (\text{R} = \text{H, Me, Ph}) \end{array} $			
Entry	Starting material (135)	Product (136)	Yield ^[a] (%)
1	 <p>135a</p>	 <p>136a</p>	92
2	 <p>135b</p>	 <p>136b</p>	87
3	 <p>135c</p>	 <p>136c</p>	91
4	 <p>135d</p>	 <p>136d</p>	90
5	 <p>135e</p>	 <p>136e</p>	91
6	 <p>135f</p>	 <p>136f</p>	93
7	 <p>135g</p>	 <p>136g</p>	83

[a] (*E*):(*Z*) ratios of products were not stated in the original publication.

A modified version of Corey's protocol,²¹³ where the DABCO additive was substituted with DBU, was reported by Hirama²⁴² for the synthesis of the ABCD ring system of ciguatoxin, whereby allylic ether **137** was isomerised to its corresponding enol ether **138** (Scheme 76, eq 1). A similar reaction was also utilised by Hirama²⁴³ as part of the synthesis of a *trans*-fused polycyclic ether skeleton (Scheme 76, eq 2).

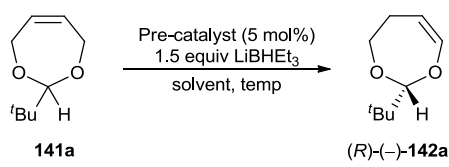
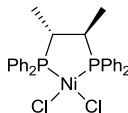
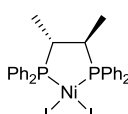
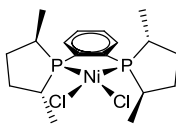
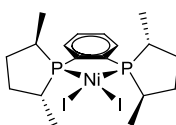


In 2002, Cossy²⁴⁴ reported that Grubbs' second generation metathesis catalyst (**45**) could be used to carry out isomerisation reactions of allyl/homoallyl ethers and *N*-allyl amines, with full *N/O*-deprotection mediated by subsequent acid-catalysed hydrolysis (Scheme 77). By omission of the hydrolysis step, certain classes of vinyl ether (and enamine) could be isolated, whilst the procedure is also applicable to homoallylic ethers.



Following on from his earlier work,²⁴⁵ Frauenrath²⁴⁶ reported greatly improved enantioselectivities for the asymmetric desymmetrisation of cyclic allyl acetal **141a**, using chiral nickel(II) complexes, to afford a vinyl acetal in up to 98% ee (Table 11, entry 7). Acceptable ee's of 90% were obtained for analogous acetals featuring isopropyl and *n*-butyl substituents using the same nickel(II) catalyst.

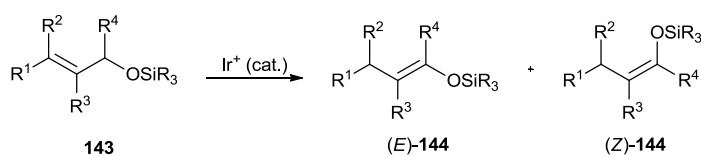
Table 11. Asymmetric isomerisation of 4,7-dihydro-1,3-dioxepin **141a** using (*R,R*)-(+)-CHIRAPHOS- and (*R,R*)-(-)-Me-DuPHOS-modified nickel complexes.

					
Entry	Pre-catalyst	Solvent	Temp (°C)	Conv'n (%) / Time (h)	ee (%)
1		THF	20	100(71)/48	67
2		THF	20	100/48	73
3		THF	-40	100(83)/72	82
4		Toluene	20	80/96	85
5		Toluene	20	100/2.5	80
6		Toluene	-20	100/48	92
7		Toluene	-55	100(74)/72	98

2.6.2 *O*-Allyl silyl ethers

Transition metal-catalysed isomerisation of allyl silyl ethers constitutes an efficient route to silyl enol ethers, that avoids the use of a stoichiometric amount of a strong base. It also enables access to both geometric isomers, thus expanding the synthetic utility of these synthetically useful enolate equivalents.

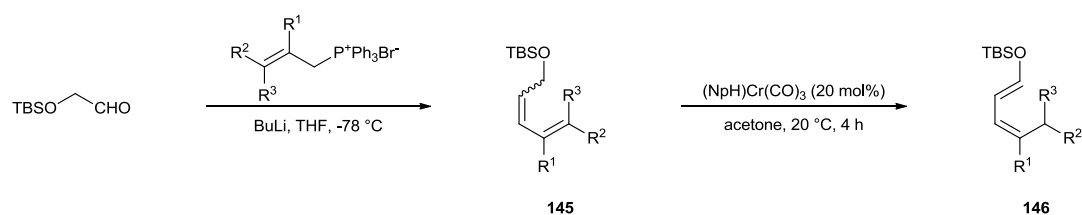
In 1979, Suzuki²⁴⁷ reported that treatment of allyl silyl ethers with $[\text{RuH}_2(\text{PPhMe}_2)_4]$, $[\text{RuH}_2(\text{PPh}_2\text{H})_4]$, $[\text{RuH}_2(\text{PPh}_2\text{Me})_4]$ or $[\text{RuH}_2(\text{PPh}_3)_4]$ complexes resulted in isomerisation to afford mixtures of (*Z*)- and (*E*)-silyl enol ethers. Almost two decades later, Miyaura^{248,249} applied $[\text{Ir}(\text{PMePh}_2)_2(\text{COD})]\text{PF}_6$ for the isomerisation of allyl silyl ethers to afford their corresponding silyl enol ethers in higher yields with better (*E*):(*Z*) ratios, under milder conditions. Isomerisation reactions of primary silyl ethers were found to favour formation of their (*E*)-isomer, with selectivities well above 90% in most cases (Table 12). For secondary silyl ethers, the (*E*):(*Z*) ratios were found to be more modest, although substrates featuring branched alkyl groups in their allylic 2-positions yielded *cis*-enol ethers in >99% geometric purity (entries 5 – 8).

Table 12. Isomerisation of primary and secondary allyl silyl ethers (**143**).

Entry	Allyl silyl ether (143)	[Ir(COD)(PMePh ₂) ₂]		[Ir(COD) ₂]PF ₆ /2PPr ₃	
		Yield (%)	<i>(E)</i> : <i>(Z)</i>	Yield (%)	<i>(E)</i> : <i>(Z)</i>
1		78	99:1	74	99:1
2		84	97:3	92	99:1
3		91			
4		87	94:6		
5		76	98:2	77	96:4
6		<10		85	88:12
7		84	68:32		
8		96	96:4	95	63:37
9				83	12:88
10				93	1: >99
11		trace		96	1: >99

Exploiting the discovery of the ability of (arene)chromium tricarbonyl complexes to catalytically isomerise conjugated dienes²⁵⁰ at room temperature via a 1,5-hydrogen shift pathway, Shibasaki²⁵¹ developed a procedure for the synthesis of silyl dienol ethers **145** for use as substrates in Diels-Alder reactions (Table 13).

Table 13. Synthesis and isomerisation of various [(silyloxy)methyl]butadiene derivatives.

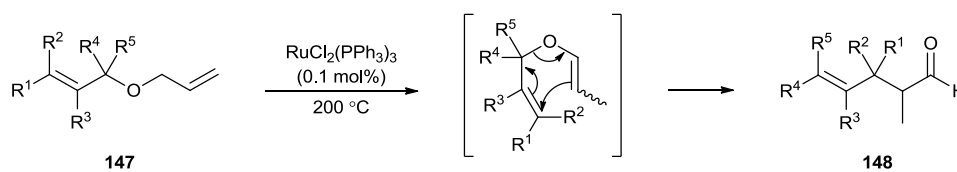


Entry	Substrate (145)	Yield (%)	(Z):(E)	Dienol silyl ether (146)	Yield (%)
1		70	87:13		86
2		61	71:29		70
3		82	83:17		80
4		53	82:18		82
5		88	81:19		58

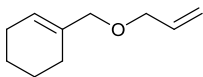
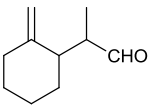
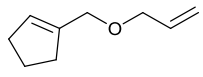
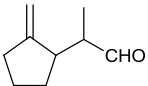
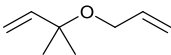
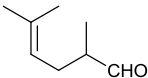
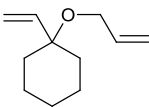
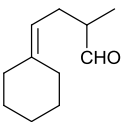
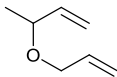
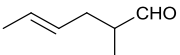
2.6.3 Isomerisation-Claisen Rearrangement (ICR)

The Claisen rearrangement of allyl vinyl ethers constitutes a valuable synthetic strategy for the preparation of γ,δ -unsaturated aldehydes and ketones,²⁵² although preparation of the required allyl vinyl ether substrates is often difficult. A convenient and versatile method for their preparation consists of transition metal-catalysed isomerisation of diallyl ethers to form allyl vinyl ethers, followed by a thermal [3,3] sigmatropic rearrangement. The term isomerisation-Claisen rearrangement (ICR) reaction has been coined to describe this process, an early example of which was reported in 1977 by Salomon.²⁵³ A series of unsymmetrical diallyl ethers **147a-i** were treated with 0.1 mol% $\text{RuCl}_2(\text{PPh}_3)_3$ at 200 °C in the absence of solvent (Table 14), with regioselective 1,3-hydrogen migration and subsequent Claisen rearrangement of the resulting allyl vinyl ethers leading to the formation of γ,δ -unsaturated carbonyl compounds **148a-i**.

Table 14. ICR reactions of substituted bis(allyl) ethers **147a-i**.

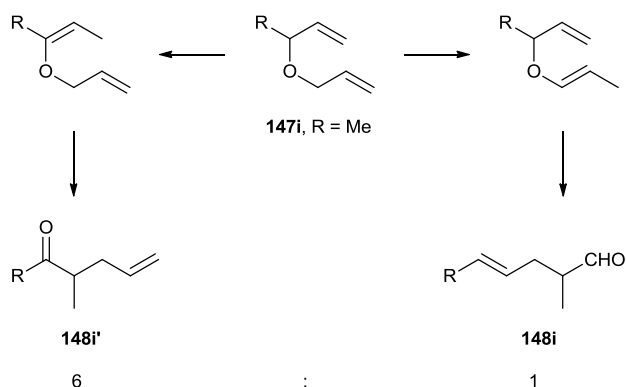


Entry	Substrate	Product	Reaction time (h)	Isolated yield (%)	GC purity (%)
1			1	92	89
	147a	148a			
2			1	90	99
	147b	148b			
3			1.5	71	100
	147c	148c			
4			3	56	70 ^[a]
	147d	148d			

Entry	Substrate	Product	Reaction time (h)	Isolated yield (%)	GC purity (%)
5			1.5		95
	147e	148e			
6			1.5	84	93
	147f	148f			
7			4	80	92
	147g	148g			
8			2	78	83
	147h	148h			
9			4	55	100
	147i	148i			

[a] Also isolated: Δ^3 -cyclopentenyl methylallyl ether and methylallyl alcohol.

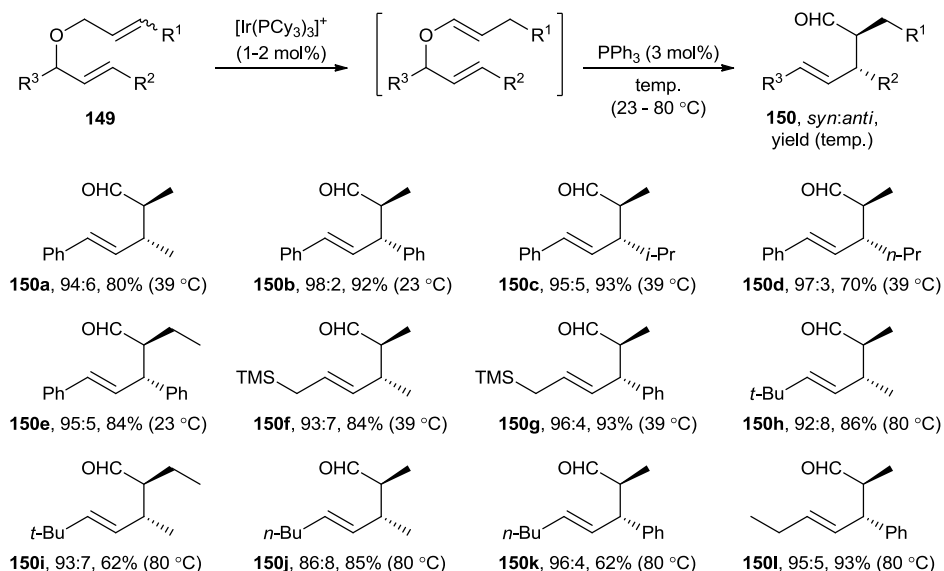
Clearly, in the cases of diallyl ethers **147g/147h**, only one of the two alkenes present migrates to form an allyl vinyl ether, that then rearranges to afford a single product. The products observed from ICR reactions of diallyl ethers **147a-f** correlate with the order of relative reactivity for alkene migration, which is generally considered to be: monosubstituted > 1,2-disubstituted > 1,1'-disubstituted > trisubstituted, reflecting the stabilities of the parent alkene. In the case of ether **147i**, which features two monosubstituted alkenes, isomerisation of the α -methylallyl ether is disfavoured to a surprisingly large extent, with the two competing rearrangement products **148i** and **148i'** being formed in a ratio of 6:1, respectively (Scheme 78).



Scheme 78. Competing products formed from an isomerisation-Claisen rearrangement of a diallyl ether **147i**.

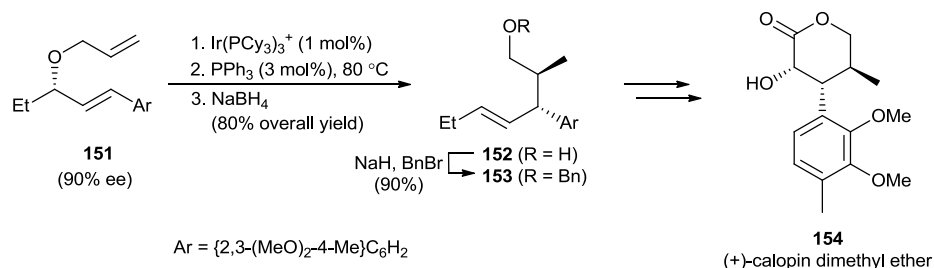
Modifications to the diallyl ether isomerisation-Claisen rearrangement (ICR) protocol have since been reported that proceed at significantly reduced reaction temperatures. For example, Ishii²⁵⁴ reported an iridium-catalysed ICR procedure in 2000, using a PCy₃ co-catalyst and reaction temperatures of 100 °C. Although these protocols allow facile access to γ,δ -unsaturated carbonyl compounds from easily prepared allyl homoallyl or bis(allyl) ethers, in all cases the products were obtained as diastereoisomeric mixtures. Chiral information is normally faithfully transcribed during [3,3] sigmatropic rearrangements due to the six-membered transition states through which they occur. Non-selective isomerisation reactions that form mixtures of (*E*)- and (*Z*)-vinyl ether isomers were therefore proposed to be responsible for the formation of diastereoisomeric *syn/anti* mixtures in these Claisen-rearrangement reactions.

Highly diastereoselective ICR reactions have been developed by Nelson and co-workers,²⁵⁵ who reported the first *syn*-selective example in 2003. The catalyst [Ir(PCy₃)₃]BPh₄ was used for the stereoselective isomerisation-rearrangement of a range of diallyl ethers, forming their corresponding *syn*-2,3-dialkyl-4-pentenal derivatives with excellent levels of diastereocontrol (Scheme 79). Ether substrates bearing a variety of substituents at their carbinol (R³) and allylic (R²) positions gave their corresponding Claisen products with consistently high (92 – 98%) *syn*-selectivity and almost exclusive formation of (*E*)-enal γ,δ -unsaturated isomers.



Scheme 79. *Syn*-selective ICR reactions of substituted bis(allyl) ethers. Isolated yields are reported for the primary alcohols derived from $i\text{Bu}_2\text{AlH}$ reduction of the initial aldehyde products **150a–l**.

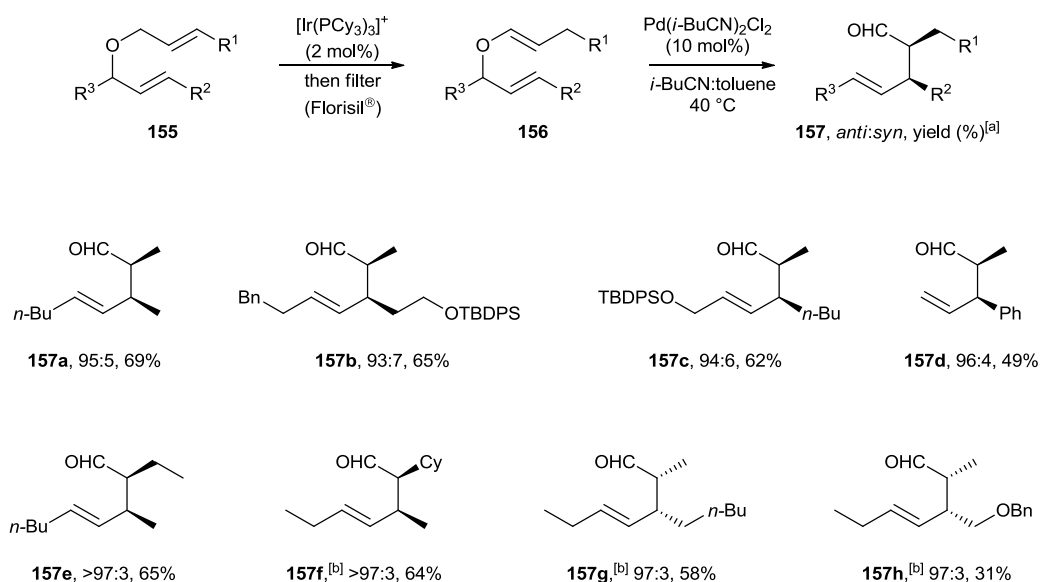
The high (*E*)-selectivity that is characteristic of iridium-catalysed allyl ether isomerisations allowed (*E,E*)/(*E,Z*)-mixtures of diallyl ethers **149e** and **149i** to be converted into rearrangement products with excellent levels of *syn*-selectivity. The synthetic utility of this method was demonstrated by its application for the asymmetric synthesis of (+)-calopin dimethyl ether **154** (Scheme 80).²⁵⁶



Scheme 80. Natural product synthesis *via* an iridium-catalysed diastereoselective ICR reaction.

In 2008, Nelson²⁵⁷ reported *anti*-selective ICR reactions of several allyl vinyl ethers that are complimentary to their *syn*-selective thermal counterparts. By combining the established iridium(I)-catalysed diallyl ether isomerisation reaction with palladium(II)-catalysed Claisen-rearrangement, a range of *anti*-2,3-disubstituted-4-pentenals could be formed with consistently high selectivities (Scheme 81). This protocol was also extended

to ICR reactions of chiral diallyl ethers (**155f-h**), with minimal erosion of their stereochemical purity during the rearrangement step. In contrast to the thermally induced Claisen rearrangement, control of vinyl ether geometry was not a pre-requisite for the formation of a stereodefined product. Vinyl ethers which were prepared as mixtures of (*E*)- and (*Z*)-isomers (**156e-f**) reliably delivered *anti*-products, presumably due to the reaction conditions facilitating facile interconversion of these geometric isomers.



Scheme 81. *Anti*-selective ICR reactions of substituted bis(allyl) ethers.

[a] Isolated yields over two steps.

[b] Reactions carried out using enantioenriched diallyl ethers **155f-h** proceeded with 97-99% retention of chirality to afford aldehydes **157f** (84% ee), **157g** (86% ee) and **157h** (92% ee).

The *anti*-selectivity of the palladium(II)-catalysed rearrangement was rationalised by a bidentate mode of coordination of the substrate to the metal centre, leading to a boat-like transition state (Figure 3) and subsequent transfer of chirality to the products.

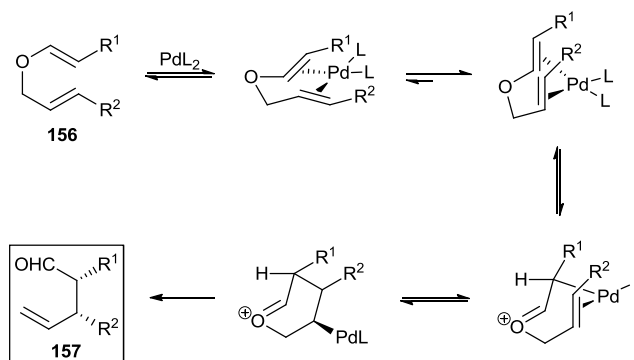
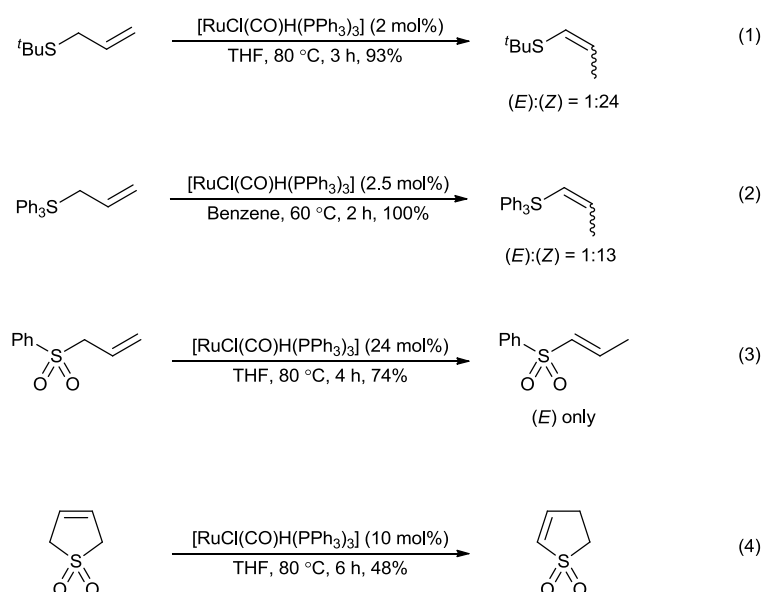


Figure 3. Postulated mechanism for Pd(II)-catalysed Claisen rearrangements.

2.6.4 Isomerisation of *S*-allyl sulphides and sulfoxides

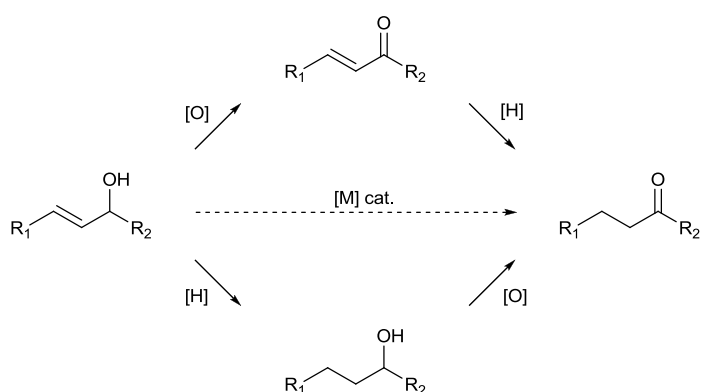
Isomerisation of *S*-allylic compounds to their corresponding vinylic species is not normally carried out using transition metal catalysts, due to rapid poisoning of the catalyst. However, a rare example of transition metal-catalysed isomerisation of *S*-allylic compounds to their 1-propenyl counterparts using $\text{RuCl}(\text{CO})(\text{PPh}_3)_3$ was reported in 2003 by Kuźnik.²⁵⁸ Attempted isomerisation of phenyl allyl, ethyl allyl and diallyl sulphide substrates resulted in very little isomerisation occurring due to competitive carbon-sulphur bond cleavage and the formation of catalytically inactive species. The best yields of isomerised products were obtained using *tert*-butyl allyl sulphide and trityl allyl sulphide (Scheme 82, eqs 1 and 2, respectively) where the steric bulk surrounding the sulphur atom is likely to inhibit coordination to the ruthenium centre. Allylic sulphones (Scheme 82, eqs 3 and 4) also gave comparatively good yields for formation of their corresponding vinylic isomers, probably due to the absence of donatable electron lone pairs at sulphur. For those substrates that undergo isomerisation, high levels of conversion to the (*Z*)-isomer were observed, with selectivity decreasing over time, implying that (*Z*)/(*E*) isomerisation was occurring after the initial double bond migration. However, immediately terminating the reaction when >99% of the starting material had been consumed enabled isomerised products to be obtained in high geometric purity.



Scheme 82. Ruthenium-catalysed isomerisation of *S*-allyl systems.

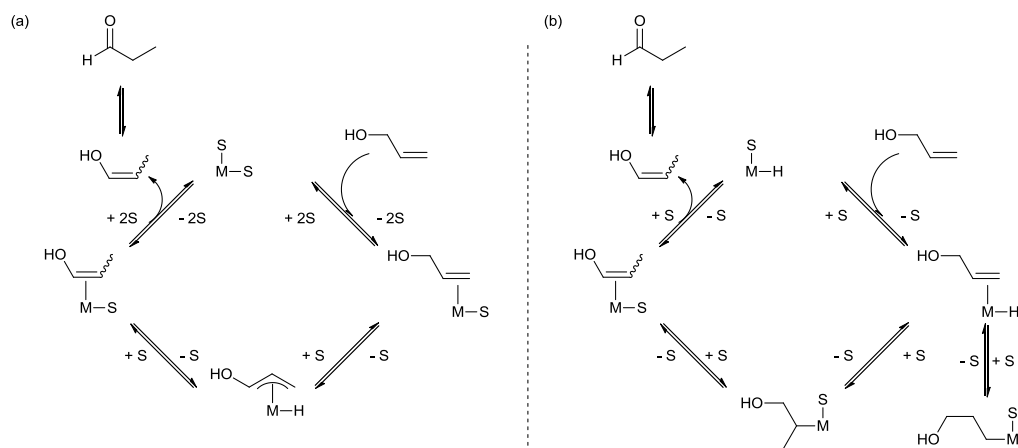
2.6.5 Isomerisation of allylic alcohols to carbonyl compounds

A recent review of allylic alcohol isomerisation, that also includes coverage of 1,3-rearrangement reactions and propargylic alcohol isomerisations, has been published by Gimeno.²⁵⁹ Previously, two highly detailed reviews of this area have been published by Bouwman²⁶⁰ and Grée.²⁶¹ The transition-metal catalysed isomerisation reactions of allylic alcohols constitutes a potentially convenient shortcut to carbonyl compounds, whose preparation might otherwise require a two-step sequential oxidation/reduction protocol (Scheme 83). This conversion is achieved *via* a one-step internal redox reaction, enabling the use of expensive and/or toxic oxidising reagents to be avoided.



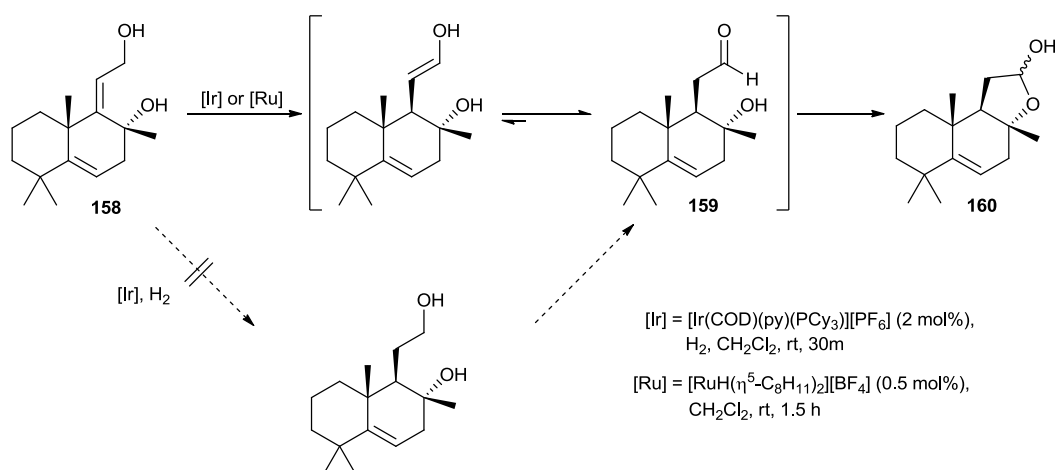
Scheme 83. Isomerisation of allylic alcohols represents a convenient shortcut to carbonyl compounds.²⁶²

Two main mechanisms have been proposed for this reaction (Scheme 84); firstly, sequential addition-elimination of a metal-hydride species, M–H, to form an enol which subsequently tautomerises. Alternatively, association of the alkene bond with a metal centre bearing two vacant coordination sites is followed by formal oxidative addition of a C–H bond to yield a π -allylmetal hydride species, that undergoes reductive elimination to form a coordinated enol that tautomerises to its keto form upon decomplexation from the metal centre. Because the carbonyl compound is thermodynamically more stable than the unsaturated alcohol, allylic alcohols generally afford ketones/aldehydes as single products.²⁶⁰



Scheme 84. (a) π -Allylmetal hydride mechanism. (b) Metal-hydride addition-elimination mechanism. (S = $2e^-$ vacant site or labile ligand).¹⁴³

A representative example of this type of isomerisation occurred during an attempt to carry out the hydroxyl-directed hydrogenation of the alkene bond of **158** with Crabtree's catalyst (Scheme 85). Instead of alkene hydrogenation occurring, the use of this catalyst resulted in stereoselective isomerisation of the allylic alcohol **158** to afford aldehyde **159**, which was subsequently isolated as a lactol (**160**).²⁶³



Scheme 85. OH-directed isomerisation of allylic alcohol **158** to afford lactol **160**.

Recent challenges addressed in this area have been broadening the substrate scope of catalysts and the development of enantioselective reactions. In 2006, Crochet²⁶² reported the use of a ruthenium phosphite catalyst to isomerise a range of trisubstituted allylic

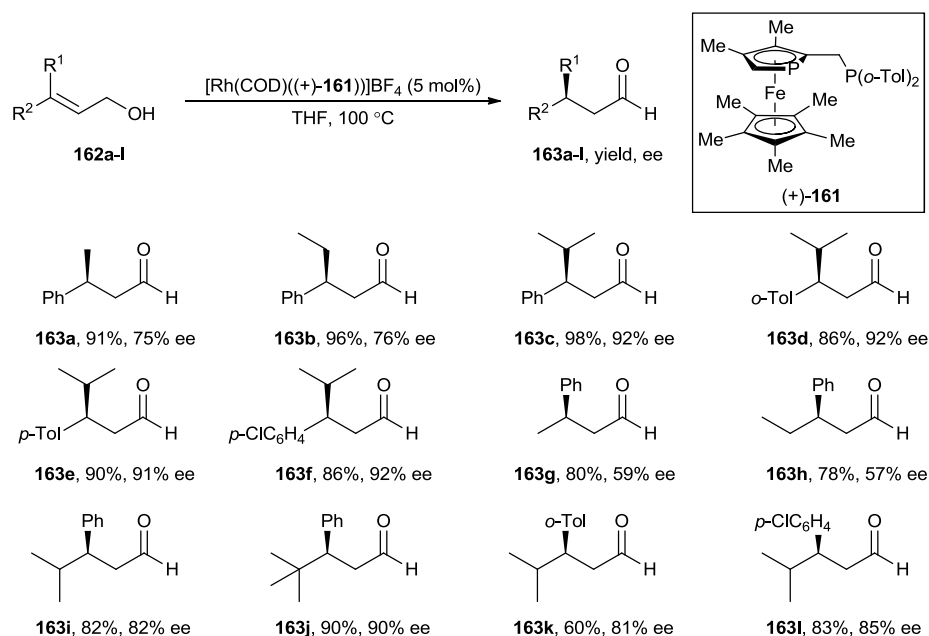
alcohols that were known to be particularly unreactive toward previously described catalyst systems (Table 15). Mono- and disubstituted allylic alcohols were also converted to carbonyl compounds, in ~99% yield, at ambient temperatures and low catalyst loadings.

Table 15. Isomerisation of different types of substituted allylic alcohols.

$$\text{R}^1\text{-CH=CH-CH(R}^2\text{)-OH} \xrightarrow[\text{THF, 35 } ^\circ\text{C}]{\text{[RuCl}_2\{\text{P(OEt)}_3\}(\eta^6\text{-}p\text{-cymene)] (5 mol\%), KO}^t\text{Bu (25 mol\%)}} \text{R}^1\text{-CH}_2\text{-CH(R}^2\text{)-C(=O)R}^3$$

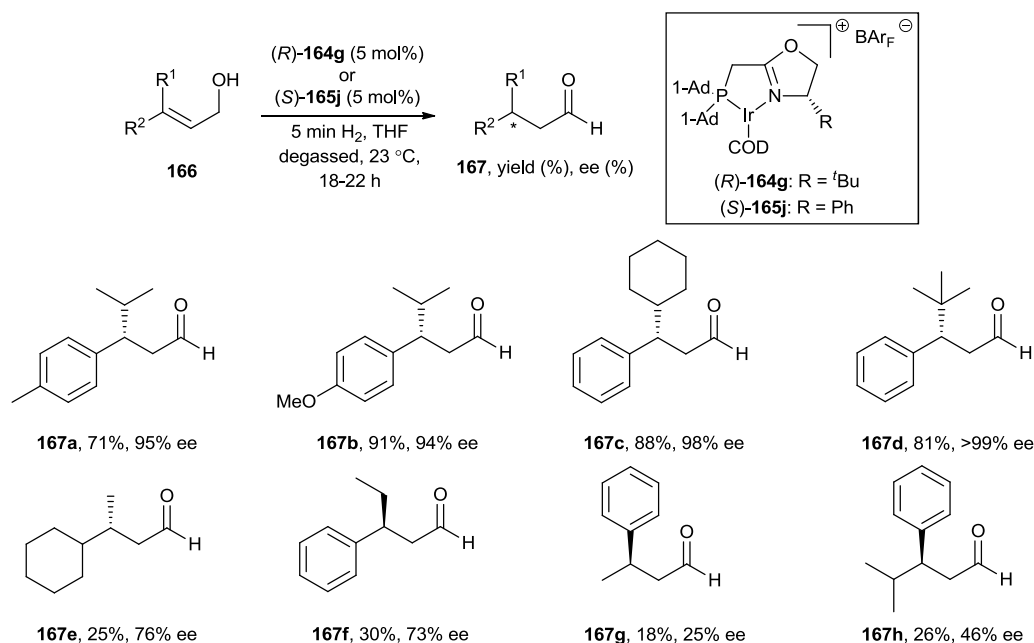
Entry	Substrate	T (°C)	Time (m)	Yield (%)	TOF (h ⁻¹)
1		35	5	99	238
2		75	10	99	494
3		35	10	99	119
4		35	5	97	233
5		35	35	99	34
6		35	50	99	24
7		35	25	99	48

An example of asymmetric allylic alcohol isomerisation was reported by Fu^{264,265} in 2001 (Scheme 86), which constituted a significant improvement upon the previous best results of 53% ee and 47% yield.^{83,210}



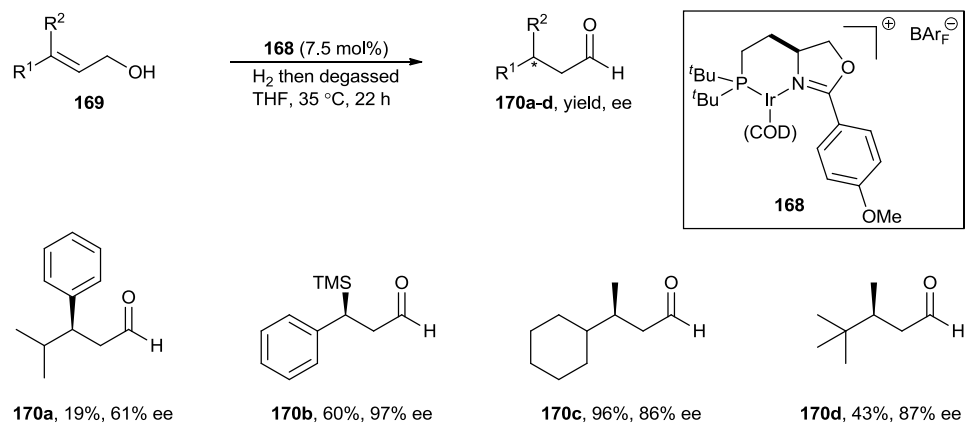
Scheme 86. Asymmetric allylic alcohol isomerisation. Aldehydes **163a-f** derived from their corresponding (*E*)-allylic alcohols; aldehydes **163g-l** derived from their corresponding (*Z*)-allylic alcohols.

Recently, Mazet^{266,267} has reported high levels of stereoselectivity during asymmetric redox isomerisation of primary allylic alcohols to aldehydes, using iridium-based catalysts (Scheme 87). The lower ee's obtained from isomerisation of the (*Z*)-allylic alcohols **166g** and **166h** were shown to be a consequence of a competing (*E*)/(*Z*)-isomerisation pathway.



Scheme 87. Asymmetric isomerisation of 3,3-disubstituted allylic alcohols.

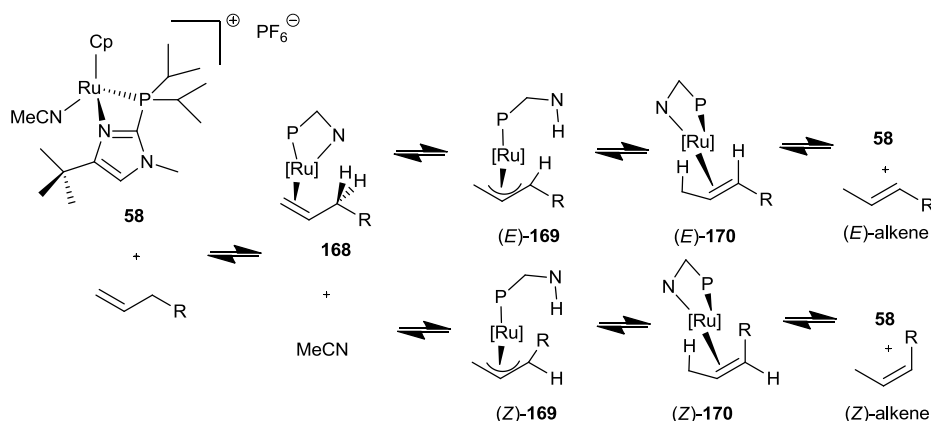
Mazet²⁶⁸ has also reported greatly improved selectivity, towards (Z)-configured and aliphatic allylic alcohols, using an analogous iridium-based catalyst **168** (Scheme 88).



Scheme 88. Improved asymmetric isomerisation of (Z)-configured and aliphatic allylic alcohols.

2.7 Catalysts capable of mediating multiple isomerisation reactions

In 2007, Grotjahn¹⁴⁷ reported the synthesis and reactivity of ruthenium(II) complex **58** as a catalyst capable of mediating multiple isomerisation reactions (see Table 16, below). A range of analogous complexes were screened, with **58** found to be the best catalyst, which efficiently isomerised a range of both functionalized and unfunctionalized alkene substrates at low catalyst loadings, affording (*E*)-alkenes in high purity. Scheme 89 depicts the proposed mechanism of the catalyst's activity: the first step in the catalytic cycle involves displacement of an acetonitrile ligand by the substrate alkene, with the basic nitrogen of the imidazole ligand then deprotonating its allylic position to afford **169**. Transfer of a proton from nitrogen to either end of the allyl moiety then either reforms the complex **168**, or effectively isomerises the alkene bond one position along the carbon chain.

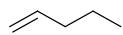
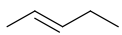
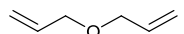
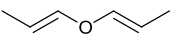
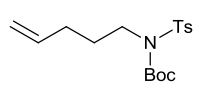
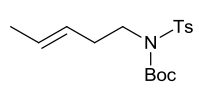
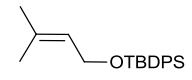
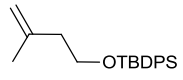
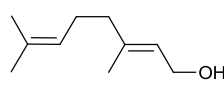
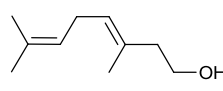
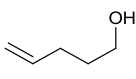
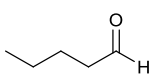
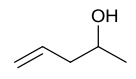
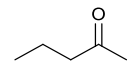
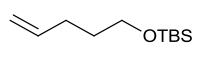
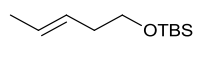
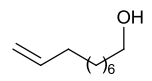
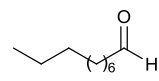
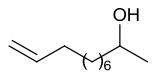
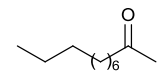
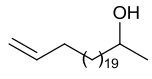
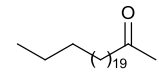
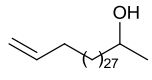
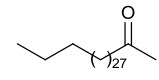


Scheme 89. Mechanistic hypothesis for the isomerisation activity of **58**.

Although most reactions were not optimised, the remarkable ability of **58** to isomerise a variety of heterofunctionalised alkene-derivatives, with high levels of (*E*)-selectivity and at low catalyst loadings, is summarised in Table 16. Particularly impressive is the double isomerisation of diallyl ether (entry 2), with neither Claisen rearrangement of the intermediate allyl vinyl ether, or detectable amounts of the (*E,Z*)-species being present. This provides ready access to a relatively unexplored class of compounds which had previously been prepared as mixtures using strong base.²⁶⁹ Unsaturated alcohols were also

efficiently isomerised to afford their corresponding saturated carbonyl compounds *via* tautomerisation of an intermediate enol species (entries 6, 7, 9–12).

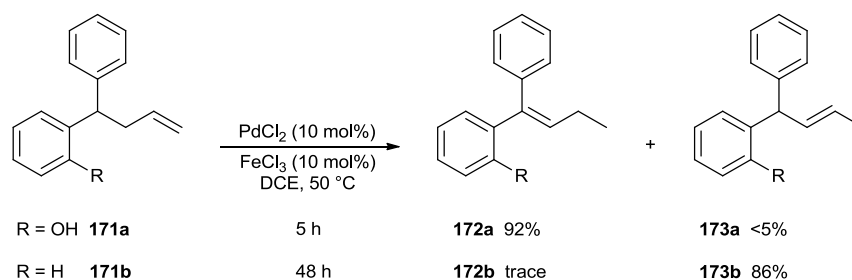
Table 16. Scope and limitations of catalyst **58**.

Entry	Reactant	Product	58 (mol%)	Temp (°C)	Time	Yield (%)
1			2	25	15 m	95
2			2	25	40 m	96
3			2	25	4 h	75 ^[b]
4			2	25	26 h	70:30 ^[a]
5			2	25	4 d	61 ^[b]
6			2	70	1 h	95
7			2	70	1 h	97
8			5	70	4 h	90
9			5	70	4 h	84
10			5	70	4 h	97
11			20	70	3.6 d	91
12			30	70	3 d	81

[a] Equilibrium ratio reached from either side within 2 – 4 h using 2 mol% of **58** at 70 °C.

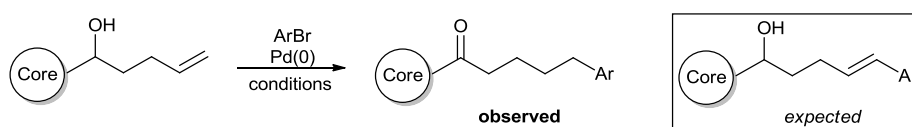
[b] Unreacted starting material (29%) and an unidentified isomer (10%) also present.

In 2009, Wang²⁷⁰ reported the effect of the presence of an *ortho*-phenol group upon the course of palladium-catalysed isomerisation reactions of alkenyl side chains. Treatment of substituted phenol **171a** with 10 mol% of palladium(II) chloride and iron(III) chloride resulted in formation of an isomeric alkene **172a** in 92% yield (Scheme 90). The same reaction conditions, when applied to **171b**, that lacks a hydroxyl group, failed to afford more than trace amounts of the corresponding trisubstituted alkene **172b**, instead resulting in migration of the alkene bond through just one bond to form **173b**.



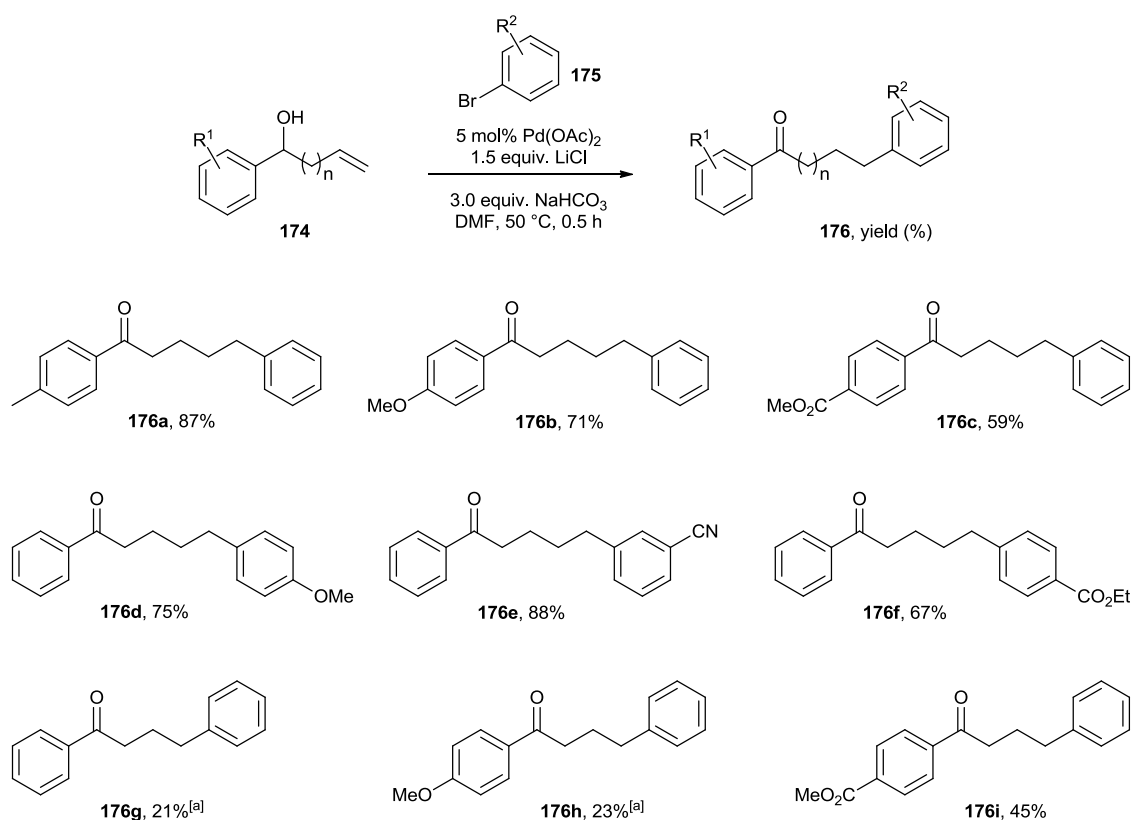
Scheme 90. The influence of an *ortho*-phenol hydroxyl group on palladium-catalysed alkene isomerisation reactions.

Tandem Heck coupling-alkene isomerisation to form carbonyl compounds has been frequently reported as a result of reactions between allylic²⁷¹ or homoallylic alcohols²⁷² and aryl halides. After formation of the cross-coupled product, a palladium hydride species mediates isomerisation of the alkene bond by reversible hydropalladation and β -hydrogen elimination. Subsequent formation of an enol, which rapidly tautomerises to the corresponding carbonyl compound, can act as an efficient thermodynamic sink to produce ketones or aldehydes as major products. However, this process is comparatively rare for reactions involving longer-chain alkenols, where products of partial isomerisation and/or regioisomeric coupling products are often obtained in significant amounts.²⁷³ The formation of ketone products via Heck-coupling of non-allylic alcohols with a range of aryl bromides, reported by Crawley²⁷⁴ in 2009, is a particularly efficient example of this type of reaction (Scheme 91).



Scheme 91. Unexpected tandem Heck-coupling/isomerisation.

As part of investigations into preparing libraries of nonsteroidal agonists of the farnesoid X receptor, Heck reactions between an aryl bromide **175** and γ -hydroxyalkene **174** were carried out to afford a range of bis-aryl ketones **176** (Scheme 92). The isomerisation reaction proved to be less efficient when the alkenyl chain was shortened, forming numerous positional isomers arising from partial isomerisation.

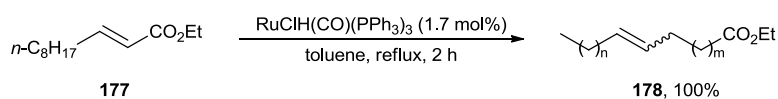


Scheme 92. Palladium-catalysed tandem Heck-isomerisation reactions.

[a] Significant amounts of positional isomers formed.

The ability of RuClH(CO)(PPh₃)₃ to isomerise a double bond out of conjugation with an electron-withdrawing group and into conjugation with another electron-withdrawing group was reported in 2000, by Mori and co-workers.²⁷⁵ Initially, treatment of α,β -unsaturated ester **177** with 1.7 mol% of RuClH(CO)(PPh₃)₃ in refluxing toluene for two hours was found to result in quantitative conversion to a mixture of non-conjugated isomers **178** (Scheme 93). This result was surprising because alkene isomerisation usually results in conversion of a less thermodynamically stable isomer into a more stable one, with α,β -

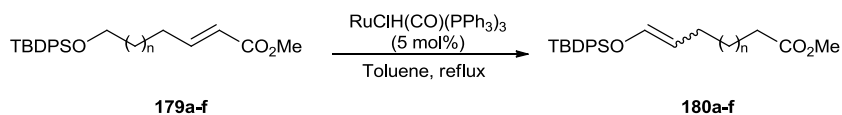
unsaturated ester **177** generally considered to be more stable than its non-conjugated counterparts.



Scheme 93. Deconjugative isomerisation of an α,β -unsaturated ester catalysed by $\text{RuClH(CO)(PPh}_3)_3$.

In order to exploit this result for the formation of other types of functionalised alkenes, isomerisation reactions of terminally functionalised α,β -unsaturated esters were carried out. A series of α,β -unsaturated esters containing a terminal silyl ether substituent were found to selectively afford their corresponding silyl enol ethers *via* isomerisation reactions mediated by the ruthenium catalyst, although the yield generally decreased with increasing length of the alkyl chain linker (Table 17).

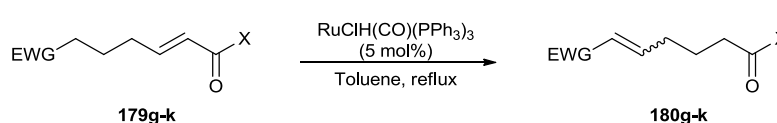
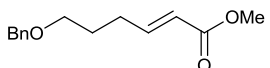
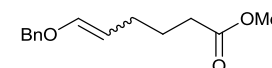
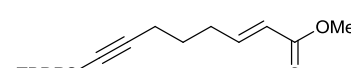
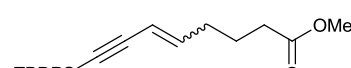
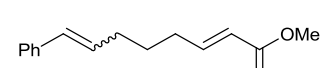
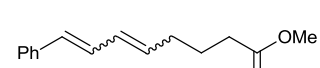
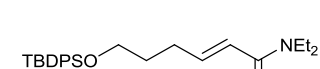
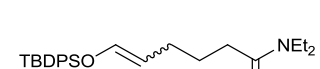
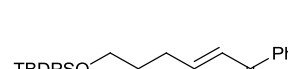
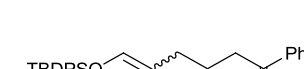
Table 17. Effect of chain length on the isomerisation of **179** to **180**.



Entry	Substrate	<i>n</i>	Time (h)	Yield of 180 (%)	(<i>E</i>):(<i>Z</i>)
1	179a	0	2	97	1:2.1
2	179b	1	2	94	1:2.2
3	179c	2	2	80	1:2.2
4	179d	3	2	85	1:2.2
5	179e	4	4	78	1:2.0
6	179f	5	4	74	1:2.1

In order to probe the scope and limitation of this reaction, a range of α,β -unsaturated carbonyl compounds featuring various electron-withdrawing groups at their termini were synthesised and subjected to the same reaction conditions (Table 18). Isomerisation was found to proceed smoothly in each case, forming a benzyl enol ether (entry 1), conjugated enyne (entry 2) and styrene derivative (entry 3) *via* alkene isomerisation of the parent α,β -unsaturated esters. Isomerisations of an α,β -unsaturated amide (entry 4) and ketone (entry 5) were also successful, although in the latter case extended reaction times were necessary, presumably due to the strong coordinating properties of its carbonyl group.

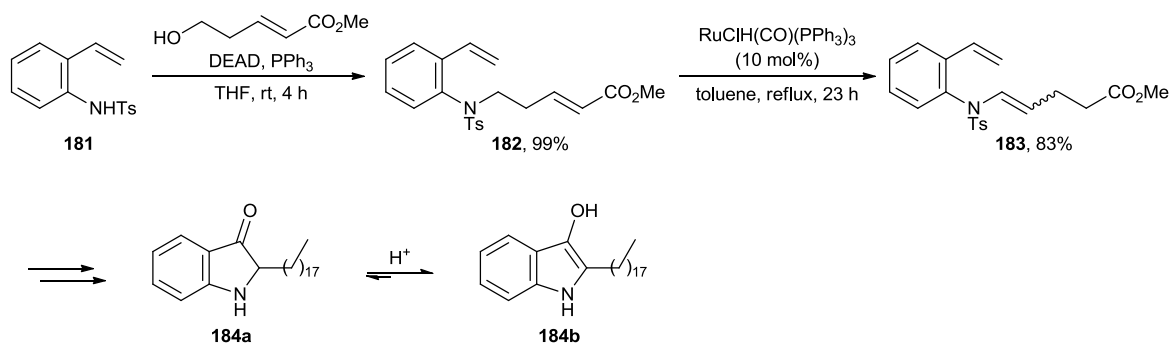
Table 18. Isomerisation of α,β -unsaturated carbonyl compounds.^[a]

				
Entry	Substrate	Product	Yield (%)	(<i>E</i>):(<i>Z</i>)
1	 179g	 180g	78	1:1.1
2	 179h	 180h	68 ^[a]	1:1.4
3	 179i^[b]	 180i	100	4.6:1
4	 179j	 180j	78	1:2.2
5	 179k	 180k	79	1:2.1

[a] Starting material was recovered in 23% yield.

[b] (*E,E*)/(*Z,E*) of **180i** = 2.2/1.

This unusual type of isomerisation-deconjugation reaction has since been utilised by Nishida²⁷⁶ and co-workers during the course of their synthesis of the reported structure of fistulosin (**184a/184b**, Scheme 94).²⁷⁷ Treatment of α,β -unsaturated ester **182** with $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$ (10 mol%) in refluxing toluene resulted in deconjugation of the alkene from the ester functionality to afford *N*-tosyl-enamine **183** in high yield.



Scheme 94. Ruthenium-catalysed deconjugative isomerisation of an α,β -unsaturated ester.

2.8 Conclusion

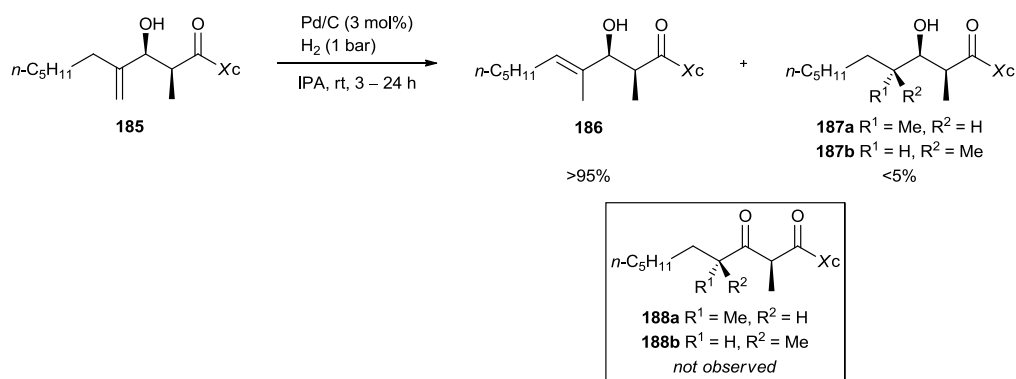
Transition metal-catalysed isomerisation reactions of alkenes are a potentially powerful class of reactions which we believe are underexploited in organic synthesis. The above review is intended to give a concise account of the range of synthetically relevant alkene isomerisation reactions that have been carried out using transition metal catalysts. In the following chapter, I will now discuss my own work in this area, namely the palladium-catalysed isomerisation of exomethylenic alcohols to afford their corresponding trisubstituted isomers. This reaction is unique because, in all other reported cases, migration of the alkene bond of an allylic alcohol results in formation of its corresponding saturated aldehyde or ketone. In the third chapter, strategies for the migration of a trisubstituted alkene bond with the simultaneous creation of a new stereogenic centre are described. In this case a chiral organoborane reagent, rather than a transition metal, was utilised. Although this novel approach for the creation of alkenes featuring chiral substituents proved not to be feasible, it did lead to the development of a novel strategy for the stereoselective synthesis of chiral 1,3-diols.

3. Isomerisation of exomethylenic allylic alcohols

This chapter describes my investigations into the synthetic utility of a novel palladium catalysed isomerisation reaction that converts exomethylenic allylic alcohols into their corresponding allylic alcohol isomers.

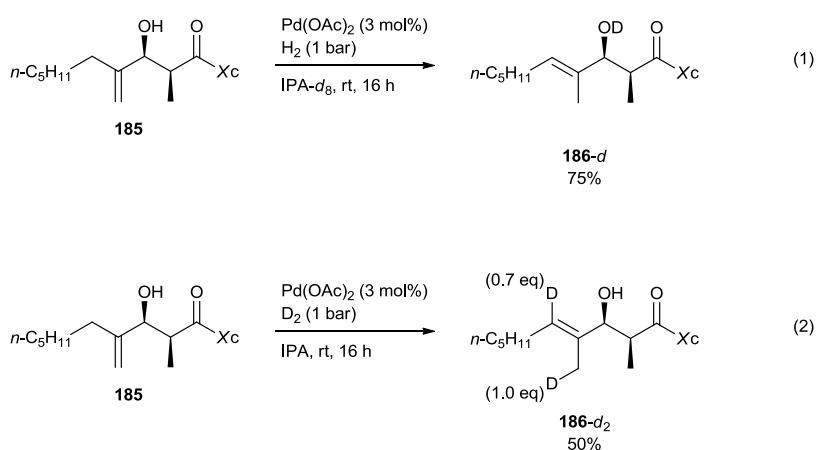
3.1 Introduction and previous work

As part of an investigation carried out by a previous member of the Bull group employing hydroxyl-directed catalytic hydrogenation reactions for the asymmetric synthesis of chiral α -methyl aldehydes,²⁷⁸ authentic samples of aldol diastereomers **187a** and **187b** were required. It was found that treatment of exomethylenic allylic alcohol **185** in IPA with Pd/C (3 mol% Pd) under one bar of hydrogen for three hours did not afford the expected diastereomeric hydrogenated products **187a/187b**, but instead gave the isomerised trisubstituted (*E*)-allylic alcohol **186** in >95% yield (Scheme 95). Neither prolonged reaction times nor increased hydrogen pressure (up to 5 bar) were found to significantly alter the product distribution. No reaction occurred in the absence of either the palladium catalyst or hydrogen gas, and substitution of palladium(II) acetate for Pd/C also gave the same product ratio of isomerised alcohol **186** to hydrogenated alcohols **187a/187b**. A variety of solvents were then screened but the only effect observed was the extent of substrate conversion, which roughly corresponded to the polarity of the solvent employed. These results were unexpected, since palladium catalysts had been used previously to reduce the alkene functionality of a number of related allylic alcohols.²⁷⁹ Importantly, products arising from migration of the alkene towards the hydroxyl group to afford an intermediate enol species that could then tautomerise to the corresponding diastereomeric ketones **188a/188b** were not observed. This was particularly surprising since palladium-catalysed isomerisation of allylic alcohols to their corresponding saturated carbonyl compounds had been reported to occur under similar conditions.²⁸⁰



Scheme 95. Palladium-catalysed isomerisation of exomethylene allylic alcohol **185** to afford trisubstituted (*E*)-allylic alcohol **186**.

The mechanism of this isomerisation reaction was subsequently investigated using palladium(II) acetate and deuterated reagents. Firstly, the reaction was performed using hydrogen gas in isopropanol- d_8 as solvent, with deuterium incorporation into the isomerised product being limited to exchange of the hydroxylic proton (Scheme 96, eq 1). Secondly, the reaction was performed using deuterium gas in place of hydrogen, which afforded a somewhat reduced yield of the isomerised product, presumably due to a kinetic isotope effect (Scheme 96, eq 2). ^1H and ^2D NMR spectroscopic analysis showed that deuterium had been incorporated into both the allylic and vinylic positions of allylic alcohol **186**.



Scheme 96. Isomerisation of exomethylene allylic alcohol **185** using deuterated reagents.

The mechanism of this isomerisation reaction was proposed as follows (Figure 4): Initial Markovnikov addition of palladium(II) deuteride across the alkene bond of **185** incorporates the first equivalent of deuterium, with subsequent β -hydrogen elimination of the resulting palladium-alkyl species **189-d** affording the monodeuterated trisubstituted (*E*)-allylic alcohol **190-d**. The mixed palladium(II) hydride species then undergoes rapid exchange with the vast excess of molecular deuterium present to afford palladium(II) deuteride, which undergoes readdition across the alkene bond of **190-d** to afford, after selective β -elimination of the hydrogen, the dideuterated product **186-d₂**. It should be noted that if the isomerisation reaction proceeded *via* an alternative π -allyl hydride mechanism then the formation of a mixture of isotopomeric products, each containing between one and four equivalents of deuterium, would have been expected.

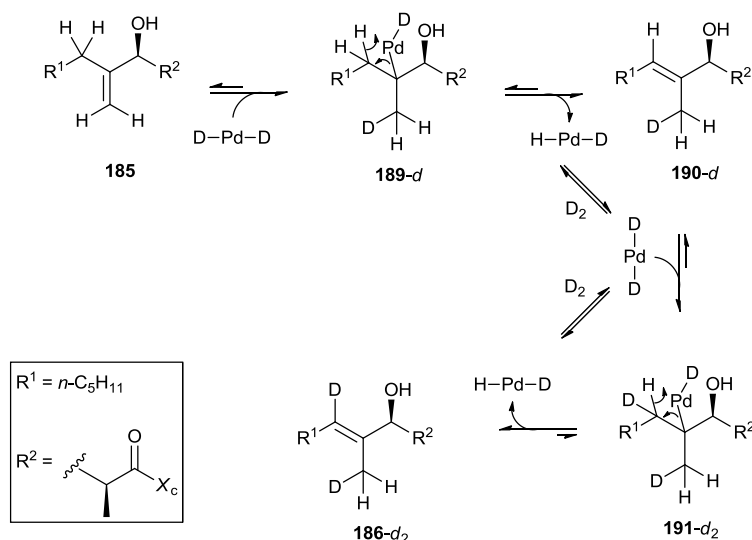
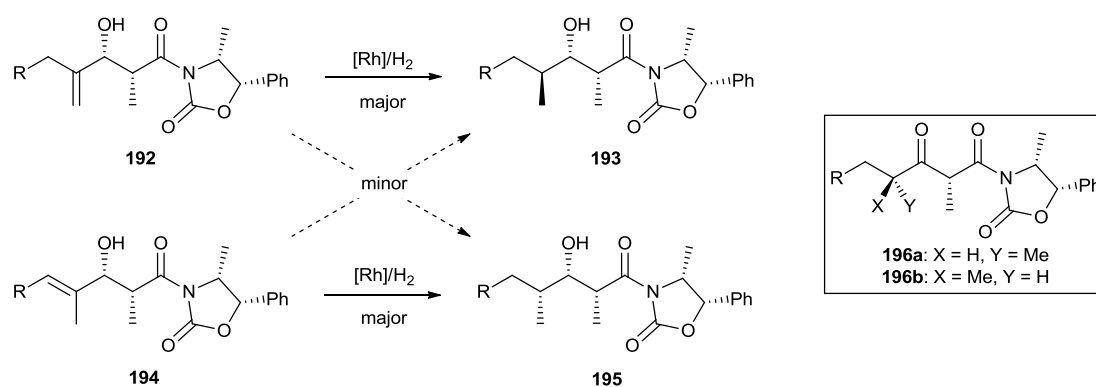


Figure 4. Proposed mechanism of palladium-catalysed isomerisation of exomethylene allylic alcohol **185** to afford trisubstituted (*E*)-allylic alcohol **186-d₂**.

Exo-methylene isomerisation reactions of related allylic alcohol substrates have also been encountered as undesired side-reactions in hydrogenation reactions by Evans,²⁸¹ who reported reduced diastereoselectivities during rhodium(I)-catalysed hydroxyl-directed hydrogenations of allylic alcohols **192** and **194** (Scheme 97). The formation of small amounts of ketonic byproducts **196a/196b**, with the observation that hydrogenation of each allylic alcohol isomer results in opposite diastereocontrol, implied that a competing alkene

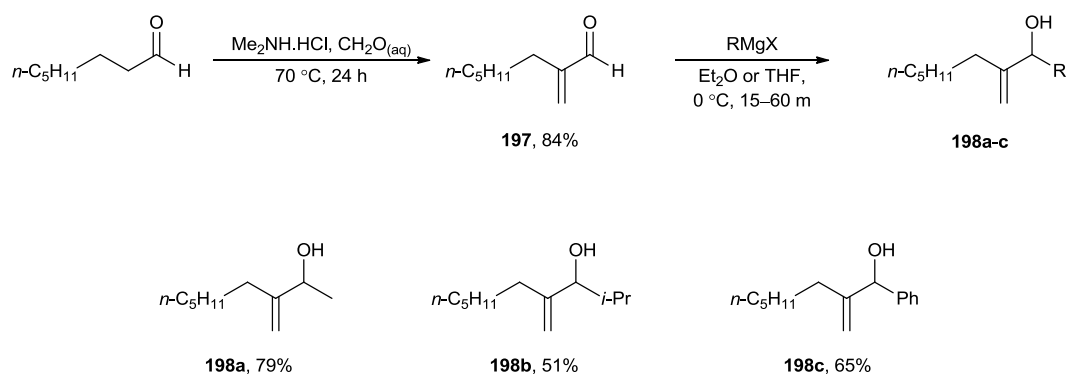
isomerisation pathway might be responsible. Prior reduction of the catalyst precursor with hydrogen gas to afford the catalytically active cationic rhodium(I) species, followed by addition of substrate **192** was found to result in extensive equilibration between the di- and trisubstituted isomeric allylic alcohols **192/194** and saturated ketones **196a/196b**. Selectivity could be restored by increasing the hydrogen pressure, which effectively suppressed the isomerisation pathway. This effect was ascribed to a change in the rate-determining step of the reaction, from addition of dihydrogen to the catalyst at low hydrogen pressure, to substrate coordination to the catalyst at high pressures of hydrogen.



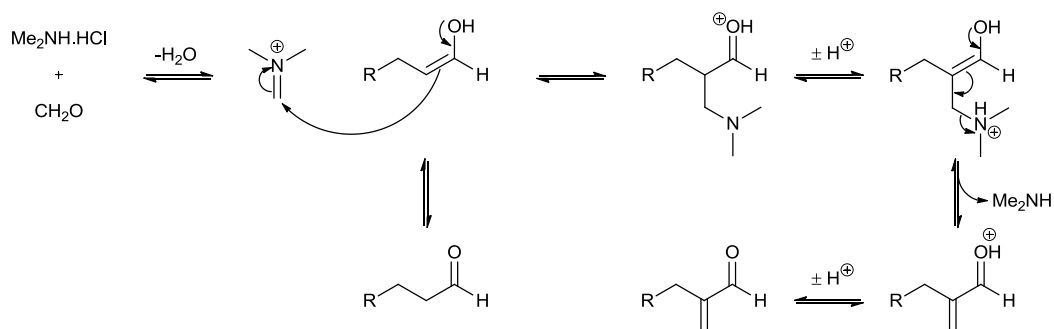
Scheme 97. Interconversion of alkenes **192** and **194** *in situ* causes low levels of diastereoselectivity in hydroxyl-directed catalytic hydrogenation reactions.

3.2 Optimisation of reaction conditions

Building upon these observations, the initial aim of my project was to determine the general applicability of this isomerisation reaction and its potential for development into a standard synthetic procedure. Accordingly, my first task was to produce a series of allylic alcohols **198a-c** as simplified analogues of **185** (Scheme 198). These compounds were easily synthesised from *n*-octanal via a Mannich-type elimination reaction²⁸² to afford an α -methylene aldehyde **197** that was then treated with the appropriate Grignard reagent.²⁸³ Formation of these products was confirmed by the presence of diagnostic resonances of the exomethylenic (at δ 4.72–5.27) and secondary alcohol fragments (at δ 3.67–5.03) in their ¹H NMR spectra.



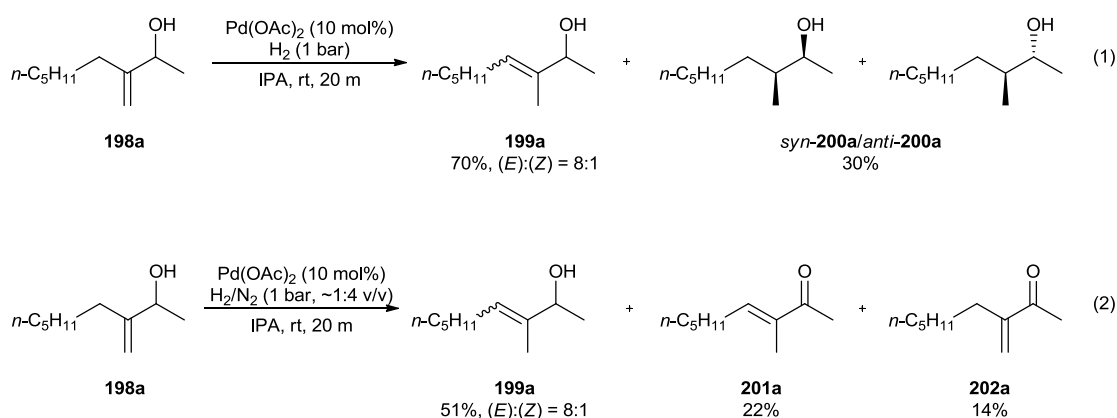
Scheme 198. Synthesis of exomethylenic allylic alcohols **198a-c** from *n*-octanal.



Scheme 99. Mechanism of the Mannich-elimination reaction.

To our delight, it was found that allylic alcohol **198a** was successfully isomerised to its trisubstituted counterpart **199a** in 70% yield upon treatment with palladium(II) acetate and hydrogen gas in isopropanol (Scheme 100, eq 1). However, a large amount of the hydrogenated alcohol species *syn*- and *anti*-**200a** (30%) was also formed under these

conditions, which meant that the alkene bond of **198a** was significantly more susceptible to hydrogenation in comparison to the alkene bond of the original aldol substrate **185**. This was presumed to be due to the reduced steric bias of the carbinol methyl group of **198a**. Similar product ratios were also obtained using various batches of palladium on carbon. Unfortunately, isomerisation experiments where a partial pressure of hydrogen was used (i.e. < 1 bar hydrogen, remainder nitrogen) in an attempt to suppress hydrogenation, whilst still allowing formation of a catalytically active palladium species, resulted in competing formation of enones **201a/202a** (Scheme 100, eq 2).



Scheme 100. Palladium(II) acetate-catalysed isomerisation reactions of allylic alcohol **198a**.

From an analytical perspective, the peaks corresponding to the alkene protons of enones **201a/202a**, the alkene and carbinol protons of the starting material **198a** and the (E)/(Z)-isomers of trisubstituted allylic alcohol **199a**, as well as the carbinol proton of saturated alcohols *syn*-/*anti*-**200a**, were all well resolved in the ^1H NMR spectrum of the crude reaction mixture (Figure 5). The ^1H NMR spectra obtained from the crude products of all subsequent isomerisation reactions using different allylic alcohol substrates were also all well-resolved and easily interpretable. Further analysis of crude product mixtures of isomerised and fully hydrogenated products could also be performed using $^1\text{H}/^{13}\text{C}$ NMR spectroscopy and mass spectrometry, as well as comparison with literature data where available. Unfortunately, chromatographic separation of the trisubstituted allylic alcohols from their corresponding saturated alcohol products was not successful, even when silver(I) nitrate-impregnated silica gel was used as a stationary phase.²⁸⁴

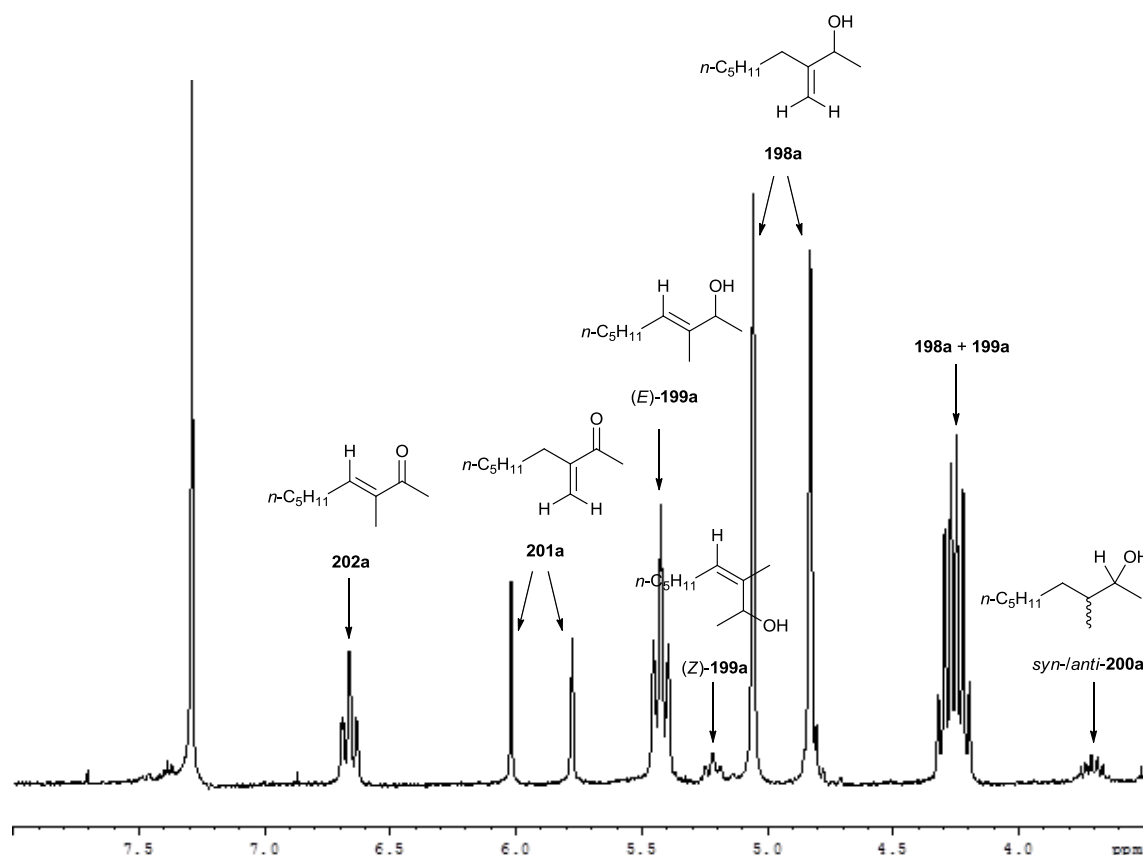
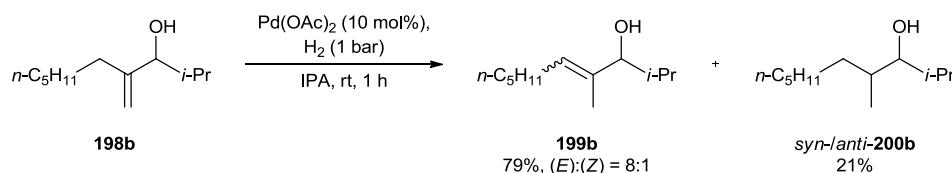


Figure 5. Representative ^1H NMR spectrum (CDCl_3) of the crude product of a partial isomerisation reaction showing resolved resonances corresponding to enones **202a** (6.68 ppm) and **201a** (5.78 and 6.02 ppm), trisubstituted allylic alcohols (*E*)-**199a** (5.43 ppm) and (*Z*)-**199a** (5.21 ppm), starting material **198a** (4.83 and 5.05 ppm) and hydrogenated alcohols *syn*-**200a**/*anti*-**200a** (3.70 ppm).

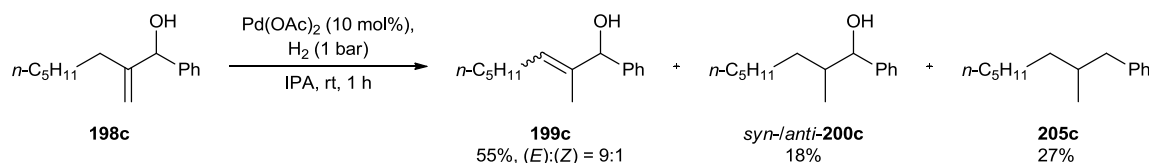
Next, allylic alcohol **198b** was treated with palladium(II) acetate and hydrogen gas (1 bar), with the presence of the more sterically demanding isopropyl group of the carbinol carbon being found to reduce the rate of the competing hydrogenation reaction, allowing formation of trisubstituted allylic alcohol **199b** in slightly higher 79% yield (Scheme 101).



Scheme 101. Palladium(II) acetate-catalysed isomerisation reaction of allylic alcohol **198b**.

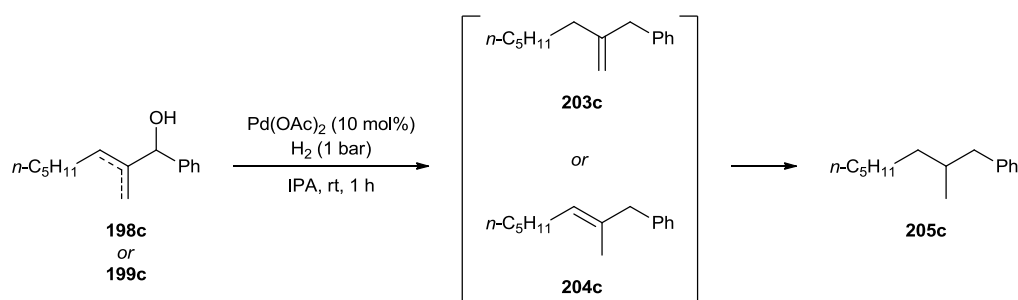
The isomerisation reaction of allylic alcohol **198c** also occurred readily to give **199c** in 55% yield, accompanied by the expected but nonetheless unwanted hydrogenated product,

200c. However, the observation of a new hydrocarbon product **205c** in the ^1H NMR spectrum of the crude post-reaction mixture was quite unexpected (Scheme 102).



Scheme 102. Palladium(II) acetate-catalysed isomerisation reaction of allylic alcohol **198c**.

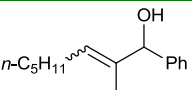
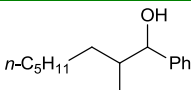
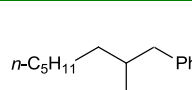
It was considered likely that protonation of the hydroxyl group from the alcohol solvent was responsible for palladium-mediated hydrogenation reactions having occurred to afford intermediate alkene species **203c** and **204c** that were then swiftly hydrogenated to give the observed alkylbenzene product **205c** (Scheme 103).²⁸⁵



Scheme 103. Formation of hydrocarbon **205c** from allylic alcohols **198c/199c**.

It was found that formation of **205c** could be suppressed either by substitution of aprotic ethyl acetate for isopropanol as solvent (Table 19, entry 2), or inclusion of caesium carbonate in the reaction mixture (entry 3). This latter protocol also resulted in an increase in the proportion of isomerised product formed, as well as a slightly higher (*E*):(*Z*) ratio.

Table 19. Methods for suppression of the formation of hydrocarbon **205c** during isomerisation of allylic alcohol **198c** (see Scheme 103).

				Product distribution (%) ^[a]		
Entry	Solvent	Cs ₂ CO ₃ (equiv.)	Time (h)	 199c	 <i>syn-/anti-200c</i>	 205c
1	IPA	0	1	55 (9:1)	15	30
2	EtOAc	0	1.5	83 (12:1)	7	10
3	IPA	1	1	80 (14:1)	20	0

[a] Values in parentheses denote (*E*):(*Z*) ratios.

From the results of these initial test reactions, **198a** was identified as being the most reactive of the three substrates and also the most prone to hydrogenation at the expense of isomerisation. Therefore, this allylic alcohol was chosen as a model substrate for optimisation of the reaction conditions. Initially, a variety of protic, polar and non-polar solvents were screened and the reaction mixtures periodically analysed by ^1H NMR spectroscopy in order to determine the amount of trisubstituted allylic alcohol present (Table 20).

Table 20. Solvent screen for the palladium(II) acetate-catalysed isomerisation reaction of allylic alcohol **198a**.

Product distribution (%) ^[a]						
Entry	Solvent	Time (m)				
1	IPA	20	70 (8:1)	30	0	0
2	MeOH	5	68 (7:1)	32	0	0
3	EtOH	15	63 (7:1)	37	0	0
4 ^[b]	<i>t</i> -BuOH	15	62 (7:1)	38	0	0
5	MeCN	3	79 (8:1)	21	0	0
6 ^[c]	THF	15	63 (7:1)	13	4	12
7 ^[c]	Acetone	10	56 (7:1)	13	6	8
8	PhMe	30	57 (5:1)	30	0	13
9	EtOAc	12	53 (5:1)	30	0	17
10 ^[c]	CH ₂ Cl ₂	10	55 (7:1)	10	3	3

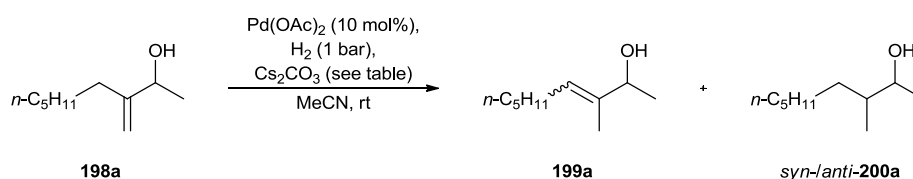
[a] Numbers in parentheses denote (*E*):(*Z*) ratios; [b] reaction carried out at 28 °C; [c] remaining mass balance comprised of starting material **198a**.

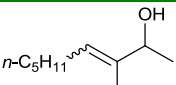
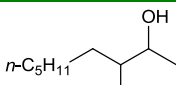
From the table, acetonitrile (entry 5) can clearly be identified as the best solvent that provides the highest selectivity towards isomerisation *versus* hydrogenation with an extremely short reaction time, followed by isopropanol which gives a greater proportion of hydrogenated product (entry 1). All other alcohols tested (entries 2–4) gave similar results to isopropanol, with a particularly fast reaction found to occur in methanol (entry 2). Interestingly, with the exception of acetonitrile, the oxidative side-reaction to afford ketone products was limited to aprotic solvents (entries 6–10). A correlation between hydrogen solubility, solvent polarity and selectivity toward isomerisation is also apparent. Firstly, the known order of increasing hydrogen solubility (at 298 K and 1 bar hydrogen pressure) in these solvents is as follows: MeCN < CH₂Cl₂ < THF < acetone < PhMe.²⁸⁶ Although this data was obtained at different pressures (>1 bar), another paper reports that the solubility of hydrogen in ethyl acetate is greater than in ethanol, which, in turn, is higher than that of methanol.²⁸⁷ Indeed, the solubility of hydrogen in *n*-alcohols (number of carbons = 1 – 4) is also known to increase with increasing alkyl chain length.²⁸⁸ The solubilities of hydrogen in ethyl acetate, toluene, isopropanol, ethanol and THF have also all been measured at a pressure of 10 bar.²⁸⁹ It can therefore be surmised that hydrogen solubility in my isomerisation reactions also increases in the following order: MeOH < EtOH < IPA < THF < PhMe < EtOAc. These trends indicate that selectivity for isomerisation over hydrogenation is favoured by a low solubility of hydrogen in the reaction solvent and a high solvent polarity. Acetonitrile and the alcoholic solvents follow this trend, although isopropanol outperforms methanol and ethanol which implies that other factors may be involved. Toluene, which was both the least polar and the worst solvent, has the second highest solubility of hydrogen and also the lowest polarity. The use of this solvent also resulted in the slowest rate of reaction, whilst the highest rates were observed in the most polar solvents methanol and acetonitrile.

Next, using acetonitrile as solvent, the beneficial effect of the caesium carbonate additive upon the isomerisation of **198a** was established. The presence of caesium carbonate was found to increase the proportion of trisubstituted allylic alcohol **199a** relative to hydrogenated product **200a**, whilst also improving the (*E*):(*Z*) ratio (Table 21). However, the overall reaction rate was observed to have decreased threefold. As the base is unlikely to interact directly with the catalyst, its most likely function is deprotonation of the hydroxyl group. The resulting alkoxide anions are likely to coordinate to the palladium

more strongly, deactivating its ability to catalyse the hydrogenation pathway relative to the isomerisation pathway.

Table 21. Establishing the influence of Cs₂CO₃ upon the palladium-catalysed isomerisation reaction of allylic alcohol **198a**.

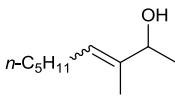
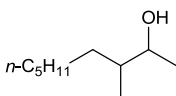


Product distribution				
Entry	Cs ₂ CO ₃ (equiv.)	Time (m)	 199a	 <i>syn-anti</i> - 200a
1	0	3	79 (8:1)	21
2	1	9	84 (10:1)	16

[a] Numbers in parentheses denote (*E*):(*Z*) ratios.

Up until this point, the amount of palladium catalyst and the substrate concentration used had been arbitrarily set at 10 mol% and 1.0 M, respectively. Upon independently varying each of these parameters, the ideal conditions for these isomerisation reactions were serendipitously found to be: 10 mol% Pd(OAc)₂, H₂ (1 bar), [substrate] = 1.0 M, Cs₂CO₃ (1 equiv.), as shown in Table 22, entry 2. It was found that a catalyst loading of 5 mol% resulted in a much slower isomerisation reaction and the formation of a larger proportion of hydrogenated product (entry 1), whereas using 20 mol% palladium resulted in a slightly less selective reaction (entry 3). Altering the substrate concentration to either 0.5 or 2.0 M was similarly found to erode selectivity levels (entries 4 and 5).

Table 22. Determination of optimum catalyst loading and substrate concentration.^[a]

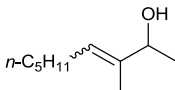
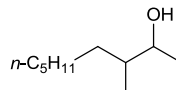
Entry	Pd(OAc) ₂ (mol%)	[Substrate] (mol dm ⁻³)	Time (m)	Product distribution (%)	
				 199a	 <i>syn-/anti-200a</i>
1 ^[c]	5	1.0	15	32 (4:1)	14
2	10	1.0	9	84 (10:1)	16
3	20	1.0	9	79 (8:1)	21
4 ^[c]	10	0.5	15	41 (7:1)	24
5 ^[c]	10	2.0	9	45	15

[a] All reactions carried out at room temperature in acetonitrile, with palladium(II) acetate (10 mol%) and caesium carbonate (1 equiv.); [b] numbers in parentheses denote (*E*):(*Z*) ratios; [c] remaining mass balance comprised of starting material **198a**.

A range of different palladium sources were then screened, with Pd(OH)₂/C identified as the catalyst of choice, followed by PdCl₂ (Table 23, entries 6 and 5, respectively). The satisfactory result obtained using Pd(OAc)₂ (entry 1) demonstrates that this isomerisation reaction can be effectively carried out under either hetero- or homogeneous catalytic conditions. However, catalyst precursors featuring strongly coordinating ligands did not produce good results. For example, the use of Pd₂(dba)₃ resulted in a relatively slow and particularly unselective reaction to afford an approximately 50:50 mixture of isomerised and reduced products (entry 2), whereas no reaction was observed at all using Pd(PPh₃)₄. Experiments at low temperatures were also carried out with mixed results. The use of palladium(II) hydroxide on carbon at 0 °C was determined to be optimal, affording trisubstituted allylic alcohol **199a** in 90% yield with an (*E*):(*Z*) ratio of 21:1 (entry 7). Lower temperatures were not found to be beneficial for this catalyst and merely increased the yield of the hydrogenated alcohols *syn-/anti-200a*. In contrast, Pd/C functioned most effectively at -10 °C to afford an 84% yield of the isomerised allylic alcohol (entry 4). The use of Pd/Al₂O₃ (5 wt%) or Lindlar's catalyst as palladium sources in isomerisation

reactions of **198a** (the latter with or without the inclusion of either quinoline or ethanethiol) did not significantly improve the selectivity toward isomerisation over hydrogenation.

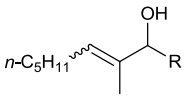
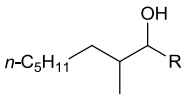
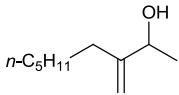
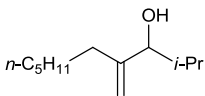
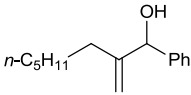
Table 23. Results of the palladium catalyst screen.^[a]

Entry	Catalyst	Temp. (°C)	Time	Product distribution (%)	
					
				199a	<i>syn-/anti-200a</i>
1	Pd(OAc) ₂	20	9 m	84 (10:1)	16
2	Pd ₂ (dba) ₂	20	1 h	54 (7:1)	46
3	Pd(PPh ₃) ₄	20	24 h	no reaction	
4	Pd/C	−10	20 m	84 (8:1)	16
5	PdCl ₂	20	20 m	87 (8:1)	13
6	Pd(OH) ₂ /C	20	10 m	88 (11:1)	12
7	Pd(OH)₂/C	0	15 m	90 (21:1)	10
8	Pd/Al ₂ O ₃	20	5 m	79 (9:1)	21

[a] All reactions performed in acetonitrile under hydrogen (1 bar) with 10 mol% palladium catalyst and caesium carbonate (1.0 equiv.); [b] numbers in parentheses denote (*E*):(*Z*) ratios.

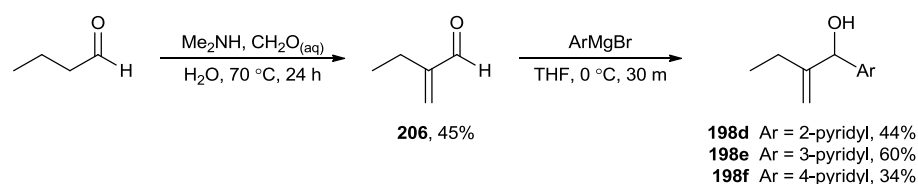
With optimised reaction conditions in hand, alcohols **198a**, **198b** and **198c** were all isomerised in high yield, with favourable (*E*):(*Z*) ratios (Table 24). As expected, the best result was achieved using **198b** as substrate. However, the maximum 96% yield of **199b** could not be improved further by performing the reaction at a lower temperature, with the proportion of unwanted hydrogenated product **200b** shown to increase at reduced temperatures.

Table 24. Isomerisation of allylic alcohols **198a-c** under the optimised conditions: [Pd] (10 mol%), H₂ (1 bar), Cs₂CO₃ (1 equiv.), MeCN.

Entry	Substrate	Catalyst (10 mol%)	Temp. (°C)	Time (m)	Product distribution	
					 199	 <i>syn-/anti</i> - 200
1	 198a	Pd(OH) ₂ /C	0	15	90 (21:1)	10
2	 198b	Pd(OH) ₂ /C	20	40	96 (17:1)	4
3	 198c	PdCl ₂	20	30	87 (8:1)	13

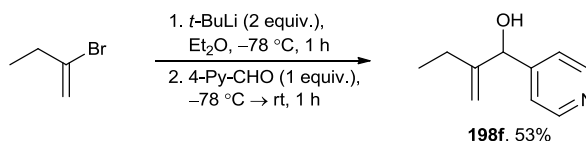
[a] Numbers in parentheses denote (*E*):(*Z*) ratios.

The scope of this isomerisation reaction was further explored by the synthesis and isomerisation of three pyridyl-substituted allylic alcohols, **198d-f**. Mannich-type α -methylenation of *n*-butyraldehyde proceeded smoothly to afford ethacrolein **206** in good yield. Using a slightly modified literature protocol,²⁹⁰ an excess of each of the desired pyridyl-Grignard reagents were then prepared *in situ* from addition of a solution of isopropylmagnesium chloride in Et₂O to the appropriate bromopyridine. Subsequent addition of ethacrolein **206** to a solution of the respective Grignard reagent gave the desired allylic alcohols **198d-f**, in unoptimised 34 – 60% yields.



Scheme 104. Synthesis of pyridyl-substituted allylic alcohols.

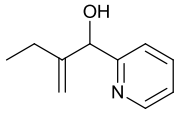
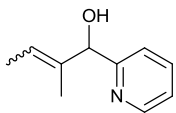
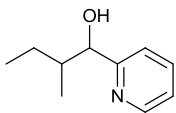
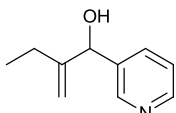
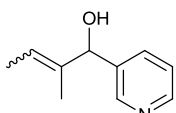
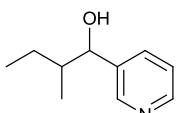
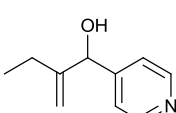
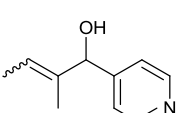
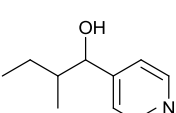
An alternative route to allylic alcohol **198f**, *via* lithiation of 2-bromo-1-butene,²⁹¹ was also successful (Scheme 105). However, the vinylic bromide required for this route was relatively expensive and as a consequence the Grignard protocol is more favoured.



Scheme 105. Synthesis of allylic alcohol **198f** from pyridine-4-carboxaldehyde.

The isomerisation reactions of allylic alcohols **198d-f** were then carried out using the optimised conditions, although isopropanol was used as solvent due to their insolubility in acetonitrile. Surprisingly, allylic alcohol **198d** (Table 25, entry 1) was preferentially hydrogenated rather than isomerised, affording its trisubstituted isomer in just 27% yield upon full conversion of starting material. The most rational explanation for this anomalous behaviour is that the ortho-pyridyl nitrogen can potentially coordinate the palladium metal and deliver it to the terminus of the alkene bond, with anti-Markovnikov addition of palladium hydride affording an intermediate which is unable to undergo isomerisation, only reversion to starting material or hydrogenation. In contrast, the 3- and 4-pyridyl substituted allylic alcohols (entries 2 and 3, respectively) underwent isomerisation reactions readily, affording their trisubstituted isomers in good yields and high (*E*):(*Z*) ratios.

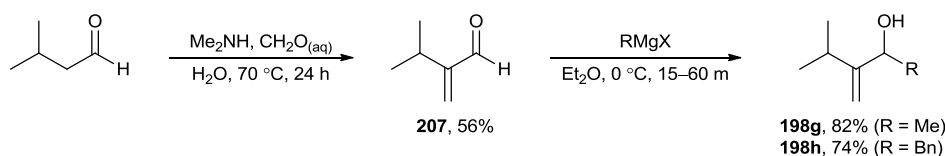
Table 25. Palladium-catalysed isomerisation reactions of allylic alcohols **198d-f**.

$ \begin{array}{c} \text{CH}_3\text{CH}_2\text{C}(\text{OH})(\text{Ar})\text{CH}=\text{CH}_2 \\ \text{198d-f} \end{array} \xrightarrow[\text{IPA, rt}]{\text{Pd(OH)}_2/\text{C (10 mol\%), H}_2 \text{ (1 bar), Cs}_2\text{CO}_3 \text{ (1 equiv.)}} \begin{array}{c} \text{CH}_3\text{CH}_2\text{C}(\text{OH})(\text{Ar})\text{CH}=\text{CH}\text{CH}_3 \\ \text{199d-f} \end{array} + \begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}(\text{OH})(\text{Ar})\text{CH}_2\text{CH}_3 \\ \text{syn-/anti-200d-f} \end{array} $				
Entry	Substrate	Time	Product distribution (%) ^[a]	
1	 <p>198d</p>	3 h	 <p>199d: 27 (13:1)</p>	 <p><i>syn-/anti-200d</i>: 73</p>
2	 <p>198e</p>	15 m	 <p>199e: 83 (10:1)</p>	 <p><i>syn-/anti-200e</i>: 17</p>
3	 <p>198f</p>	15 m	 <p>199f: 83 (10:1)</p>	 <p><i>syn-/anti-200f</i>: 17</p>

[a] Numbers in parentheses denote (*E*):(*Z*) ratios.

3.3 Isomerisation to form tetrasubstituted allylic alcohols

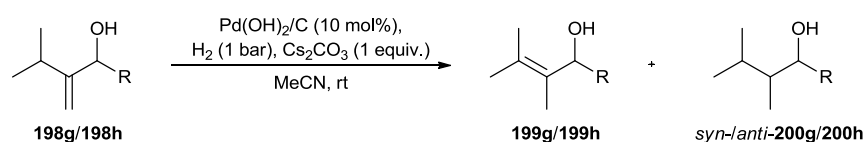
All of the isomerisation reactions described to date had produced trisubstituted alkene bonds; it was therefore decided to test the feasibility of isomerisation to form tetrasubstituted alkenes. Application of the Mannich-type α -methylenation and Grignard reactions (MeMgI, BnMgBr) to isovaleraldehyde proceeded without incident to afford alcohols **198g** and **198h** (Scheme 106).



Scheme 106. Synthesis of allylic alcohols **198g/198h**.

Application of optimal isomerisation reaction conditions to allylic alcohols **198g/198h** furnished their corresponding tetrasubstituted isomers **199g/199h** in approximately 60% yields (Table 26). The slightly reduced yields of isomerisation products may be due to the added steric requirements of the *syn*-periplanar conformation required for β -hydride elimination (see Figure 6, below).

Table 26. Palladium-catalysed isomerisation reactions of allylic alcohols **198g/198h**.



Entry	Substrate	Time	Product distribution (%)	
1	<chem>CC(C)C(=C)C(O)C</chem> 198g	15 m	<chem>CC(C)C(=C)C(O)C</chem> 199g : 61	<chem>CC(C)C(C)C(O)C</chem> 200g : 39
2	<chem>CC(C)C(=C)C(O)Cn1ccccc1</chem> 198h	25 m	<chem>CC(C)C(=C)C(O)Cn1ccccc1</chem> 199h : 58	<chem>CC(C)C(C)C(O)Cn1ccccc1</chem> 200h : 42

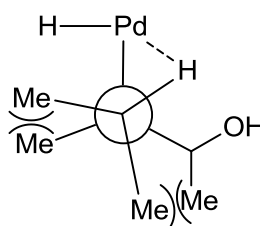
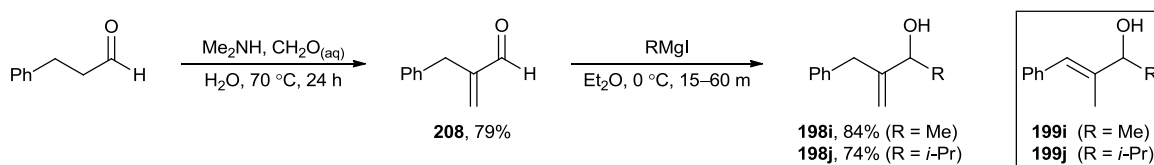


Figure 6. Steric interactions which may disfavour isomerisation to form a tetrasubstituted alkene.

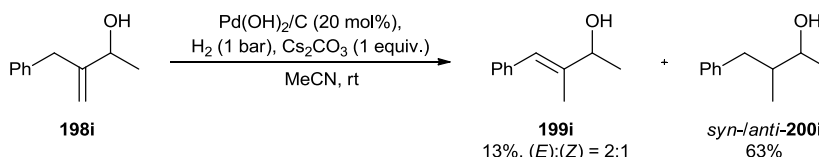
3.4 Isomerisation to form conjugated allylic alcohols

A conclusion that can be drawn about the processes occurring during these reactions is that the rate of isomerisation is fast relative to the hydrogenation pathway for both disubstituted and trisubstituted allylic alcohol substrates. If the rate constants for hydrogenation were comparable to those of isomerisation then very little, if any, isomerised products would be observed. This inspired the preparation of substrates where the alkene of the isomerised product might prove more resistant to hydrogenation, so that instead of an 'A → B → C' cascade occurring, a reaction manifold involving 'A → B *or* C' would predominate. The allylic alcohols **198i** and **198j**, easily synthesised in two steps from hydrocinnamaldehyde, seemed to fulfil this criterion since their isomerisation would lead to an allylic alcohol **199** that would be stabilised by conjugation of its alkene substituent to its aryl ring (Scheme 107).



Scheme 107. Synthesis of allylic alcohols **198i/198j** and their expected isomerisation products **199i/199j**.

Unfortunately, these substrates proved unexpectedly resistant to isomerisation and were instead gradually hydrogenated, with the amount of isomerised product present remaining consistently low throughout the reaction. The best result of only 13% yield of isomerisation product was obtained for alcohol **198i** (Scheme 108).



Scheme 108. Palladium-catalysed isomerisation reaction of allylic alcohol **198i**.

This outcome was in direct contradiction to the previous observations with allylic alcohols **198a-c**. Therefore, either (1) the products of isomerisation, with the alkene conjugated to the aromatic ring, were more readily hydrogenated; or (2) isomerisation of the starting material was slow in comparison to hydrogenation. In light of the fact that conjugated alkenes are known to be more thermodynamically stable than their isolated counterparts, the second explanation appears more reasonable.

A possible explanation for the lack of isomerisation product observed was due to potential coordination of the aromatic ring to the palladium catalyst. For isomerisation to occur, a hydrogen atom must be delivered to the terminus of the alkene in the hydropalladation step of the catalytic cycle, with the disubstituted sp^2 -carbon atom coordinated to palladium (Figure 7, path a). Subsequent β -hydride elimination from the benzylic position then generates the isomerised product. However, coordination of palladium by the phenyl ring might result in a strained transition state that cannot adopt the correct geometry to undergo elimination from the benzylic position. Alternatively, formation of **210b** might occur *via* a six-membered transition state, and this intermediate would only lead to regeneration of the starting material, or (irreversible) formation of the fully hydrogenated product **200i**.

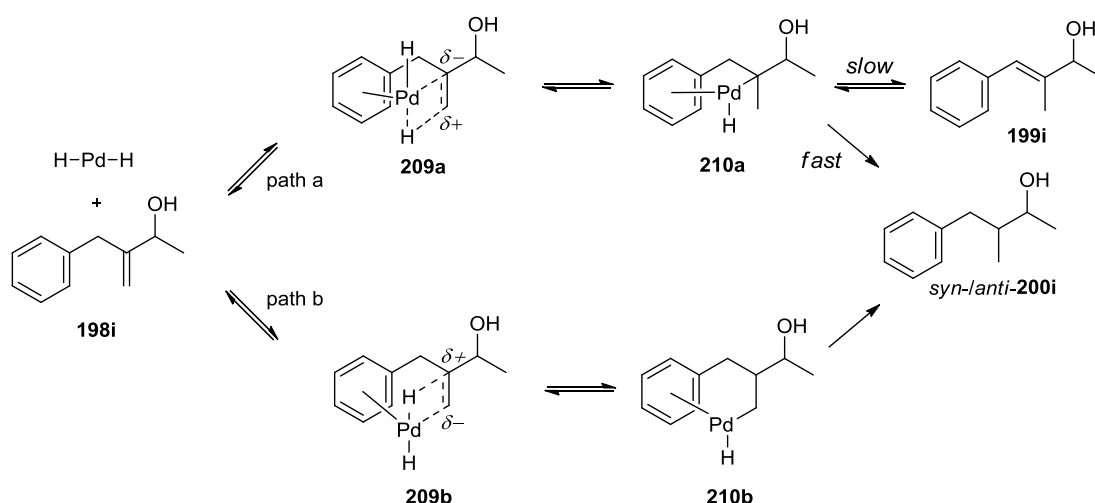
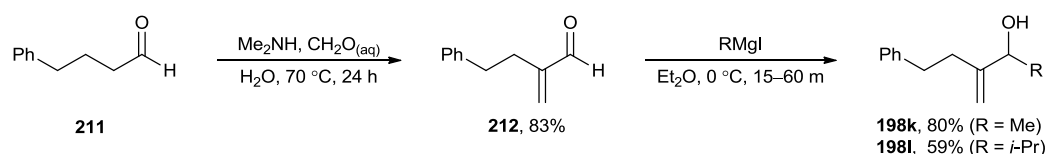


Figure 7. Hypothesised mechanism for the reduction/isomerisation of **198i**.

The four-carbon chain homologues **198k/198l** were prepared therefore from 4-phenylbutanal (**211**) using our standard Mannich-elimination/Grignard protocol (Scheme 109), in order to indirectly probe the validity of this theory.



Scheme 109. Synthesis of allylic alcohols **198k/198l**.

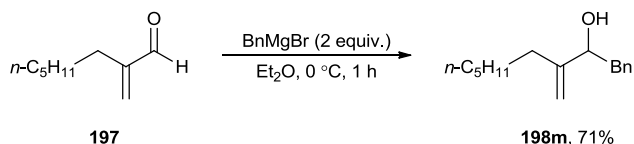
Both exomethylenic allylic alcohols **198k/198l** underwent isomerisation upon treatment with a palladium catalyst and hydrogen gas, to afford their corresponding trisubstituted allylic alcohols **199k/199l** (Table 27). The use of palladium(II) chloride was found to be optimal for isomerisation of **198k** and a slightly higher yield of isomerised product **199k** was obtained by carrying out the reaction at 0 °C (entry 2). As expected, alcohol **198l**, featuring a more sterically demanding isopropyl carbinol substituent, was found to afford a higher proportion of isomerised to reduced product (entry 3). However, the extent of isomerisation was low in comparison to the isopropyl-substituted allylic alcohol **198b**, which featured an aliphatic side-chain that gave its trisubstituted isomer in 96% yield under equivalent conditions. As the respective steric demands imposed by the *n*-hexyl and 2-(phenyl)ethyl chains would not be expected to differ significantly, an electronic effect due to aryl coordination to the catalyst may be responsible for the reduced ratio of isomerised to hydrogenated products.

Table 27. Palladium-catalysed isomerisation reactions of allylic alcohols **198k/198l**.

Entry	Substrate	Catalyst (10 mol%)	Time	Temp. (°C)	Product distribution (%) ^[a]	
1		PdCl ₂	15 m	20	 199k : 44 (13:1)	 200k : 56
2		PdCl ₂	1 h	0	 199k : 55 (6:1)	 200k : 45
3		Pd(OH) ₂ /C	1 h	20	 199l : 75 (8:1)	 200l : 25

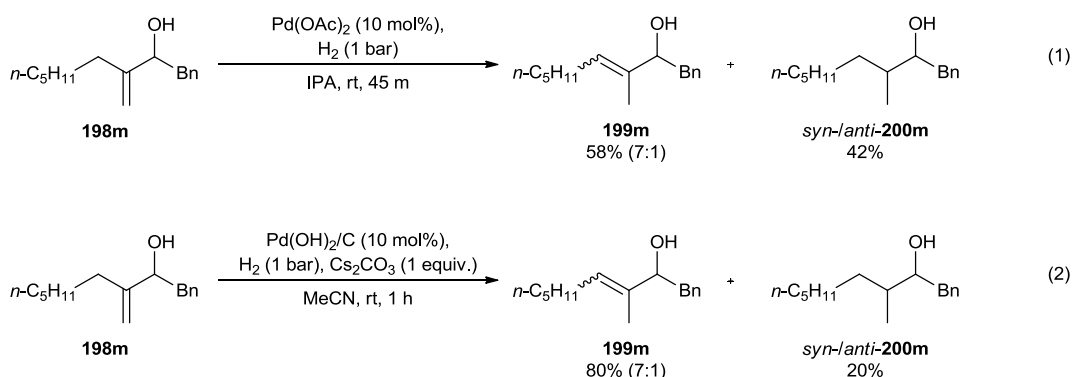
[a] Numbers in parentheses denote (*E*):(*Z*) ratios.

In order to determine whether substrates containing aromatic rings capable of coordinating to the palladium catalyst after the hydrometalation step might be generally problematic for this type of isomerisation reaction, the allylic alcohol **198m** was synthesised from aldehyde **197** and benzylmagnesium bromide (Scheme 110).



Scheme 110. Synthesis of allylic alcohol **198m**.

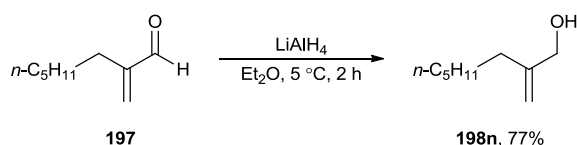
Isomerisation of **198m** under the conditions originally used to isomerise the methyl and isopropyl analogues (**198a** and **198b**, respectively) yielded an approximately 60:40 mixture of isomerised and reduced products (Scheme 111, eq 1). Based on the relative steric demands of the methyl, isopropyl and benzyl groups, the yield of **199m** observed was much lower than expected. This result once again implies that the presence of a relatively electron-rich aromatic ring that can coordinate to the metal centre is likely to adversely affect the selectivity towards isomerisation over hydrogenation. However, it should be noted that use of optimised conditions for this reaction resulted in **198m** being isomerised in relatively good yield (Scheme 111, eq 2).



Scheme 111. Palladium-catalysed isomerisation reactions of allylic alcohol **198m** under unoptimised (eq 1) and optimised (eq 2) reaction conditions.

3.5 Isomerisation reactions of primary and tertiary allylic alcohols

Since all of the substrates investigated to date were secondary allylic alcohols, it was then decided to investigate isomerisation of the primary alcohol **198n**, that was easily synthesised by reduction of aldehyde **197** using LiAlH₄ (Scheme 112).



Scheme 112. Synthesis of primary allylic alcohol **198n**.

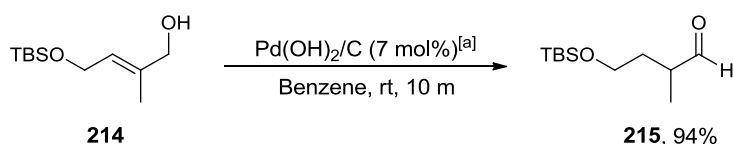
Contrary to expectations, isomerisation of this substrate (**198n**) was relatively slow, affording good yields of hydrogenated product **200n** (Table 28, entry 1). The yield of isomerised trisubstituted allylic alcohol **199n** could be raised by increasing catalyst loading (entry 2), but not by lowering the reaction temperature (entry 3). The detection of aldehyde **213** in the crude product mixture implies that the more typical mode of allylic alcohol isomerisation occurs with this substrate, i.e. formation of an enol intermediate which tautomerises to afford an aldehyde. However, production of this aldehyde by oxidation of the hydrogenated alcohol **200n** by the palladium catalyst cannot be totally ruled out.

Table 28. Palladium-catalysed isomerisation reactions of primary allylic alcohol **198n**.

198n	199n	200n	213			
Entry	[Pd(OH) ₂ /C]	Temp. (°C)	Time	Product distribution (%) ^[a]		
				199n	200n	213
1	10 mol%	20	40 m	49 (4:1)	35	16
2	15 mol%	20	15 m	65 (4:1)	21	14
3	15 mol%	0	1 h	41 (3:1)	39	20

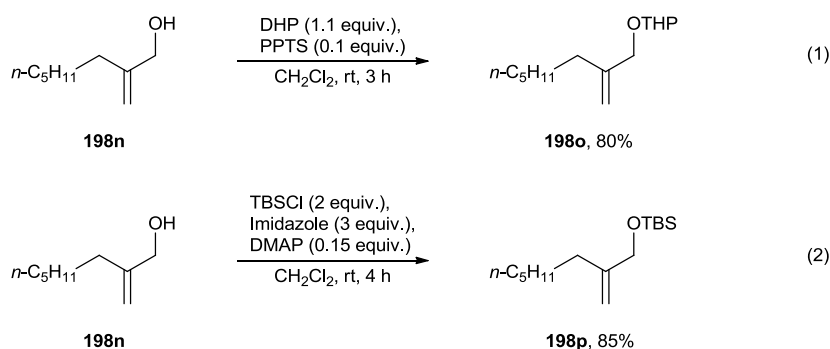
[a] Numbers in parentheses denote (*E*):(*Z*) ratios.

It should be noted that a recent report from Sabitha and co-workers²⁹² describes the use of hydrogen-activated Pd(OH)₂/C for the isomerisation of a range of primary allylic alcohols to their corresponding saturated alcohols. The facile isomerisation of allylic alcohol **214** (Scheme 113) demonstrates the ease with which this type of alcohol (i.e., **198n/199n**) undergoes this kind of isomerisation reaction. However, when isomerisation of allylic alcohol **198a** was attempted *via* pre-activation of a palladium catalyst, a similar mixture of oxidation and isomerisation products to that obtained in our studies of partial hydrogen pressures was observed (see Scheme 100, eq 2).



Scheme 113. Isomerisation of a primary allylic alcohol to afford its corresponding saturated aldehyde; [a] the catalyst was pre-activated under 1 bar H₂ for 30 m.

The THP- (**198o**) and TBS-protected (**198p**) analogues of alcohol **198n** were then synthesised (Scheme 114, eqs 1 and 2, respectively); these protecting groups were selected due to their ready removability and were intended to mimic the steric effect of a bulky substituent at the carbinol carbon. In the absence of electronic effects, this structural feature appeared to be critically important for achieving high levels of selectivity towards isomerisation over hydrogenation.



Scheme 114. Synthesis of THP-protected allylic alcohol **198o** (eq 1) and TBS-protected allylic alcohol **198p** (eq 2).

This structural design was found to significantly suppress the hydrogenation pathway and afforded higher yields of isomerised products (Table 29). However, enol ethers **216o/216p** were also formed as products of an unavoidable isomerisation side-reaction. The formation of these products also suggests that the saturated aldehyde **213** (Table 29) is formed *via* direct isomerisation of the allylic alcohol **198n** and/or its trisubstituted isomer **199n**.

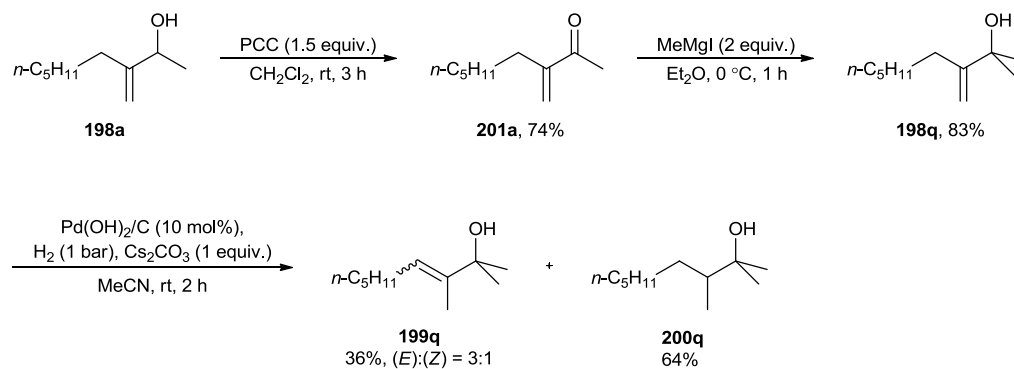
Table 29. Isomerisation of protected primary allylic alcohols.

198o/198p				199o/199p	<i>syn-/anti-200o/200p</i>	216o/216p
Entry	Substrate	Temp. (°C)	Solvent	Product distribution (%) ^[a]		
1		20	MeCN	 199o: 62 (4:1)	 <i>syn-/anti-200o:</i> 15	 216o: 23
2		0	MeCN	 199o: 70 (4:1)	 <i>syn-/anti-200o:</i> 11	 216o: 19
3		20	EtOAc	 199p: 69 (4:1)	 <i>syn-/anti-200p:</i> 23	 216p: 8

[a] Numbers in parentheses denote (*E*):(*Z*) ratios.

A tertiary alcohol **198q** was also synthesised *via* oxidation of allylic alcohol **198a** and treatment of the resulting ketone **201a** with MeMgI. However, when this allylic alcohol was subjected to the optimised isomerisation conditions, the hydrogenated alcohol **200q**

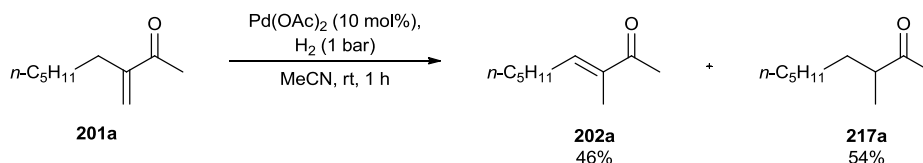
was formed as the major product in 64% yield with the isomerised product **199q** being present in only 36% yield (Scheme 115).



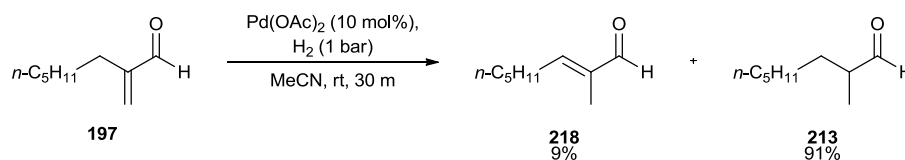
Scheme 115. Synthesis and isomerisation of tertiary allylic alcohol **198q**.

3.6 Isomerisation reactions of α,β -unsaturated carbonyl compounds

It was proposed that the alkene bonds of an enone might be less susceptible to palladium-catalysed hydrogenation than the corresponding allylic alcohol and as a consequence more isomerised product might be observed. Attempted isomerisation of the exomethylene α,β -unsaturated ketone **201a**, which was prepared by oxidation of allylic alcohol **198a**, resulted in formation of saturated ketone **217a** as the major product, with the trisubstituted α,β -unsaturated isomer **202a** also present as a minor component in the crude reaction product (Scheme 116). When the same procedure was attempted with the corresponding aldehyde **197**, very little trisubstituted α,β -unsaturated aldehyde **218** was observed, with the corresponding saturated aldehyde **213** being formed as almost the sole product of the reaction (Scheme 117). This suggests that any alkylpalladium hydride species formed in these reactions rapidly undergoes reductive elimination to afford the C–H bonds of saturated products.



Scheme 116. Palladium-catalysed isomerisation of exomethylene α,β -unsaturated ketone **201a**.

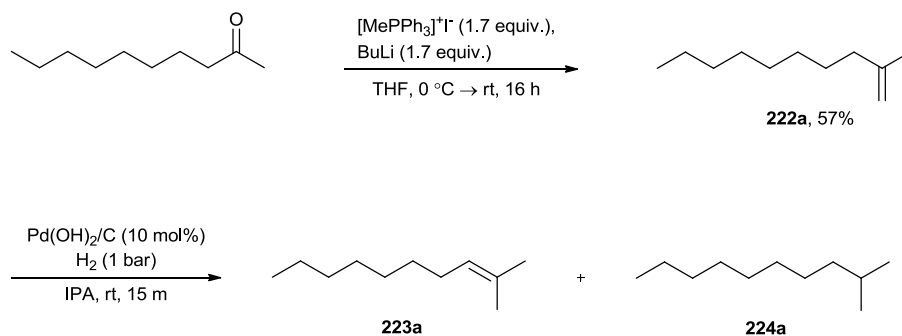


Scheme 117. Palladium-catalysed isomerisation of α -methylene aldehyde **197**.

The poor results obtained in these reactions discouraged any extension of this study to equivalent isomerisation reactions of the corresponding exomethylene α,β -unsaturated carboxylic acids and esters.

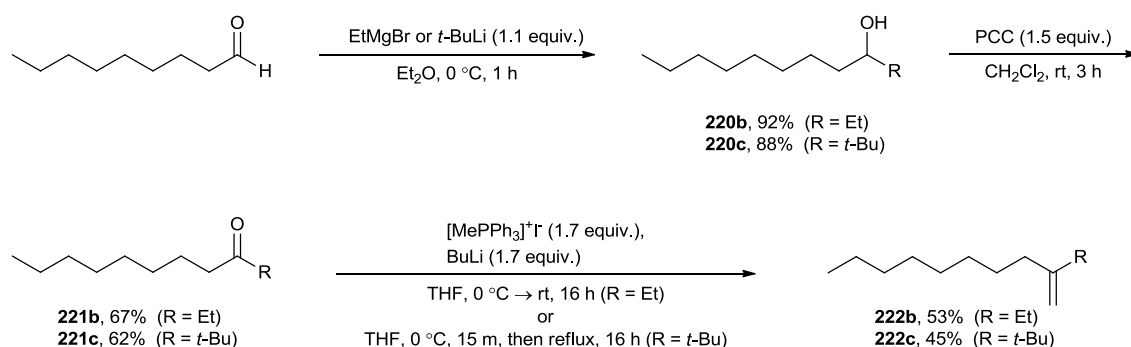
3.7 Isomerisation reactions of exomethylenic hydrocarbons

The electronic nature of the functional group appeared to exert a significant influence upon the course of the palladium-catalysed isomerisation/hydrogenation reactions, and as a consequence we were interested to determine what would happen during the isomerisation reactions of simple hydrocarbon alkenes. The exomethylene-containing hydrocarbon **222a** was synthesised *via* a methylene Wittig reaction on 2-decanone in 57% yield (Scheme 118). Interestingly, when treated with 10 mol% Pd(OH)₂/C and 1 bar of hydrogen gas, the product of isomerisation, **223a**, was obtained in good yield after a short reaction time. Hydrogenation was still a competing pathway, and at longer reaction times the proportion of saturated hydrocarbon **224a** became greater. However, as observed for allylic alcohols, this catalyst system carried out a relatively rapid isomerisation of exomethylene compound **222a** to afford its trisubstituted isomer **223a**, whilst both di- and trisubstituted alkenes undergo comparatively slow hydrogenation reactions. Other internal alkene-containing isomers that could potentially have been formed from further migration of the double bond along the chain were not observed.



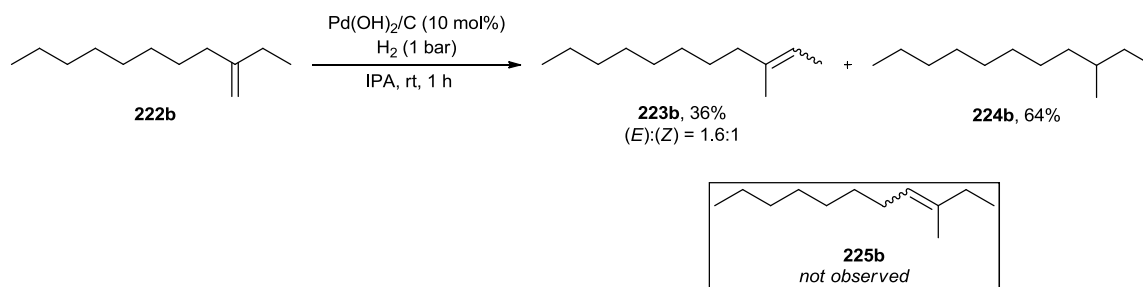
Scheme 118. Synthesis and palladium-catalysed isomerisation of exomethylenic hydrocarbon **222a**.

Encouraged by this positive result, a pair of more sterically demanding analogues **222b/222c** were prepared, featuring ethyl and *tert*-butyl substituents in place of the methyl group of **222a** (Scheme 119).



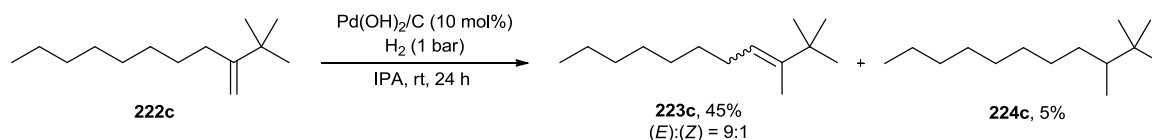
Scheme 119. Synthesis of the exo-methylene hydrocarbon series of substrates.

When treated under the same isomerisation conditions as for **222a**, the ethyl analogue **222b** reacted more slowly to afford a mixture of saturated hydrocarbon **224b** and the trisubstituted alkenes (*E*)- and (*Z*)-**223b**, which were identified from their ^1H and ^{13}C NMR signals (Scheme 120). No other alkene-containing products, including the alternative positional isomer **225b**, were detected in the ^1H NMR spectrum of the crude reaction mixture.



Scheme 120. Isomerisation of exomethylenic hydrocarbon **222b**.

Treatment of the *tert*-butyl substituted alkene **222c** under the isomerisation reaction conditions afforded a mixture of alkane **224c** and the trisubstituted alkenes (*E*)- and (*Z*)-**223c**, although in a much higher isomeric ratio (Scheme 121). The reaction of this substrate occurred considerably more slowly, with only 50% substrate conversion being achieved after 24 hours.



Scheme 121. Palladium-catalysed isomerisation of *tert*-butyl alkene **222c**.

3.8 Summary

It is clear that a combination of palladium catalyst and hydrogen gas is capable of achieving selective isomerisations of exomethylene-containing substrates to their corresponding trisubstituted isomers, without further migration of the alkene bond occurring, under mild and simple reaction conditions. Good yields and high (*E*):(*Z*) ratios were observed for the isomerisation of the majority of allylic alcohol substrates examined. Unfortunately, unavoidable competing hydrogenation reactions which proceed alongside the isomerisation result in significantly reduced yields, particularly if reaction progress is not closely monitored, resulting in mixtures of unsaturated and saturated products that are extremely difficult to separate by chromatography or distillation. The highest yields of isomerised products were obtained with substrates featuring the range of substitution patterns shown below, in Figure 8. When $R^2 = \text{alkyl}$ or $R^3 \neq \text{H}$, a larger proportion of hydrogenated alcohol products **200** were observed. Similarly, the isomerisation of a primary allylic alcohol substrate (i.e. $R^1 = R^3 = R^4 = \text{H}$, $R^2 = n\text{-pentyl}$) afforded reduced yields of trisubstituted alkene products **199**. Although yields of 51 – 80% were achieved with alcohols featuring homobenzyl substituents at position R^1 , the main pathway for hydrocinnamaldehyde-derived substrates (i.e. $R^1 = \text{benzyl}$) was hydrogenation.

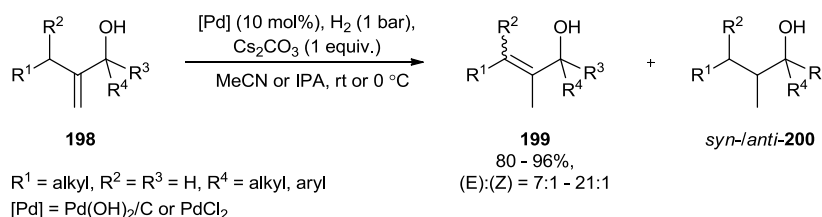


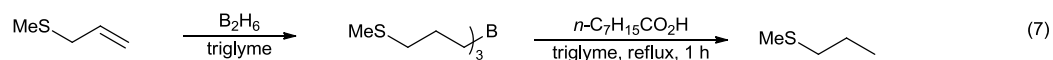
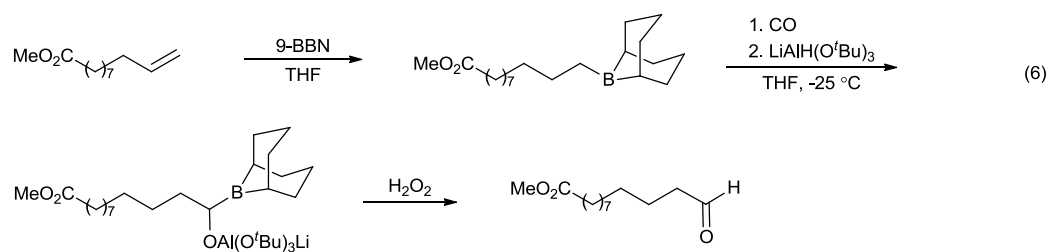
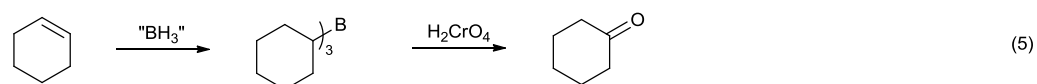
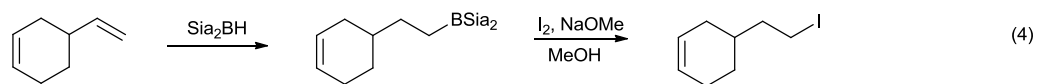
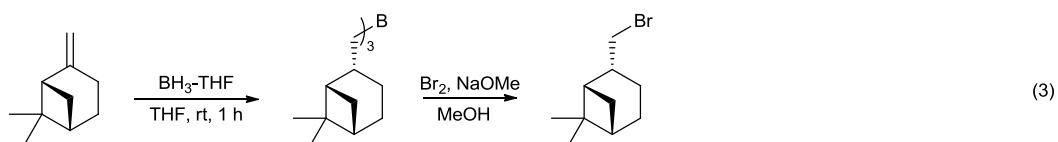
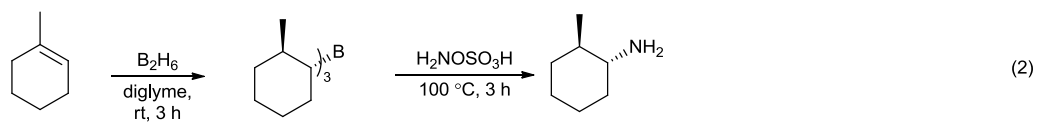
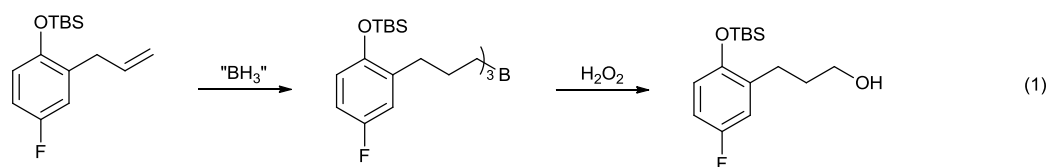
Figure 8. Substrate substitution pattern exerts a dramatic influence upon the viability of palladium-catalysed isomerisation reactions.

In the following chapter, I will now present results of my investigation into the novel use of chiral organoboranes in alkene isomerisation reactions and the development of an asymmetric hydroboration reaction of β,γ -unsaturated esters for the production of chiral 1,3-diols in good ee.

4. Synthesis of chiral aldol products using asymmetric hydroboration reactions

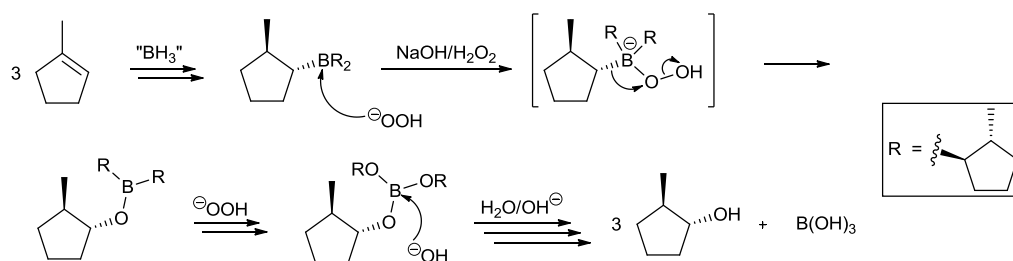
4.1 Introduction

The addition of diborane to alkene bonds, known as hydroboration, was discovered in 1956 by the late H. C. Brown,²⁹³ who subsequently devoted the rest of his career towards establishing the scope and applications of this reaction. During the course of his comprehensive exploration of the chemistry of organoboranes, it was established that (i) hydroboration of alkenes is essentially quantitative, proceeding in a *cis anti*-Markovnikov fashion to preferentially position the boron atom at the least substituted position; (ii) many other functional groups are tolerated; (iii) the reaction is reversible; and (iv) substitution of the boron atom of organoboranes with various heteroatom/alkyl groups occurs with retention of configuration. This last characteristic was largely responsible for organoboranes being established as highly versatile synthetic intermediates: they can be readily converted into alcohols,²⁹⁴ amines,²⁹⁵ bromides,²⁹⁶ iodides,²⁹⁷ ketones,²⁹⁸ homologated aldehydes²⁹⁹ or protonated with carboxylic acids³⁰⁰ to afford their formally reduced species (Scheme 122).



Scheme 122. Synthetic transformations of organoboranes obtained via hydroboration of alkenes.

The majority of these substitution processes proceed with retention of configuration by the incoming group, which occupies the precise position previously occupied by the boron atom. The mechanism of an oxidative process that converts a chiral organoborane to its corresponding chiral alcohol is shown in Scheme 123.³⁰¹ Bromination and iodination are notable exceptions, where displacement occurs with inversion of configuration at the carbon centre. These halogenation reactions of organoboranes are greatly accelerated by the presence of base, presumably due to the initial formation of an “ate” complex. Subsequent displacement of boron by the incoming halogen then results in clean inversion at the organoborane stereocentre (Scheme 124).^{296,297}



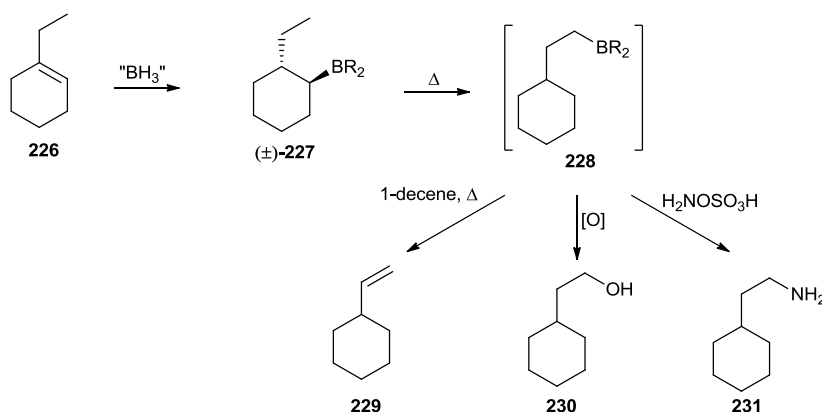
Scheme 123. Mechanism of organoborane oxidation with alkaline hydrogen peroxide.



Scheme 124. Mechanism of the base-induced reaction of bromine with an organoborane.

4.2 Alkene isomerisation reactions of organoboranes

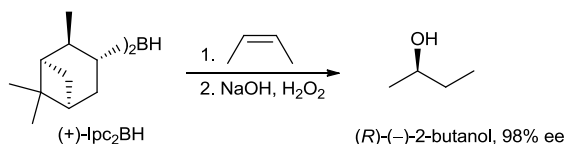
The reversible nature of the hydroboration of alkenes can potentially allow for a contrathermodynamic isomerisation of internal or endocyclic alkenes. For example, hydroboration of 1-ethylcyclohexene (**226**) readily affords a *trans*-organoborane **227**, which, upon heating, undergoes isomerisation via sequential elimination/re-addition steps³⁰² to position the boron at the terminus of the ethyl chain, thus reflecting the strong thermodynamic preference of boron to occupy the least sterically hindered position (Scheme 125). Addition of a molar excess of a higher boiling olefin to the reaction mixture, followed by heating, results in efficient displacement, thus enabling the isomerisation product vinylcyclohexane (**229**) to be distilled from the equilibrating mixture. Alternatively, the intermediate organoborane can be oxidised or aminated to afford alcohol **230** or amine **231**, respectively.³⁰³



Scheme 125. Hydroboration-isomerisation is a versatile synthetic technique for the functionalization of alkene-containing substrates.

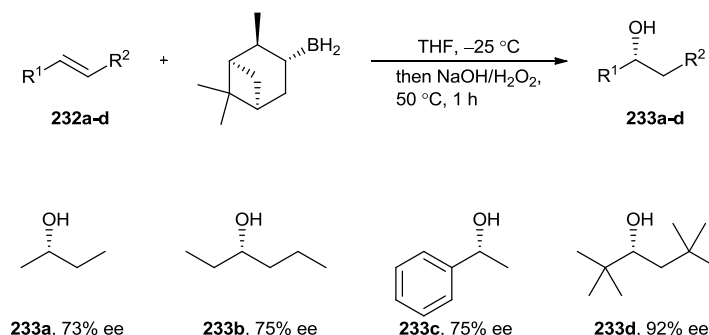
4.3 Asymmetric hydroboration reactions

Asymmetric hydroboration began with the discovery that the hydroboration product of α -pinene, diisopinocampheylborane (Ipc_2BH), was itself a highly stereoselective hydroboration reagent. Using optically pure (+)- Ipc_2BH (>99% ee), the hydroboration-oxidation of (*Z*)-2-butene afforded (*R*)-(-)-2-butanol in 98% ee (Scheme 126).^{2h,304}



Scheme 126. Asymmetric hydroboration-oxidation of (*Z*)-2-butene using (+)- Ipc_2BH .

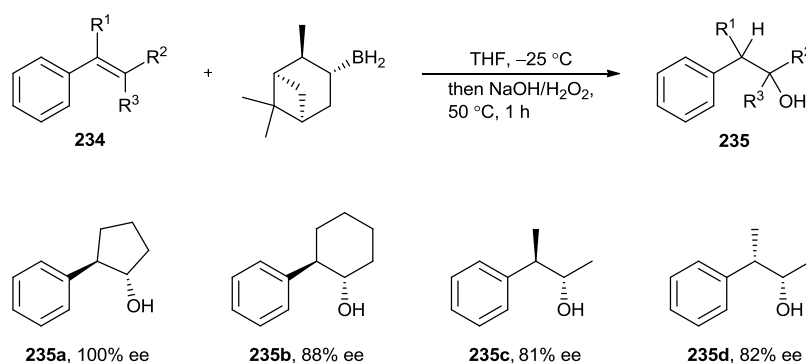
Ipc_2BH was subsequently found to hydroborate a wide range of (*Z*)-alkenes to afford, upon oxidation, the corresponding secondary alcohols with consistently high enantioselectivities.³⁰⁵ However, poorer selectivities were observed with the more sterically demanding (*E*)-1,2-disubstituted and trisubstituted olefins, with oxidation of the intermediate organoboranes affording their product alcohols in just 14 – 22% ee.³⁰⁶ For these classes of olefin substrate, the related monoisopinocampheylborane (IpcBH_2) was more appropriate, with Brown demonstrating the conversion of a range of (*E*)-1,2-disubstituted olefins into enantiomerically enriched secondary alcohols (Scheme 127).³⁰⁷



Scheme 127. Asymmetric hydroboration of (*E*)-alkenes by IpcBH_2 followed by oxidation.

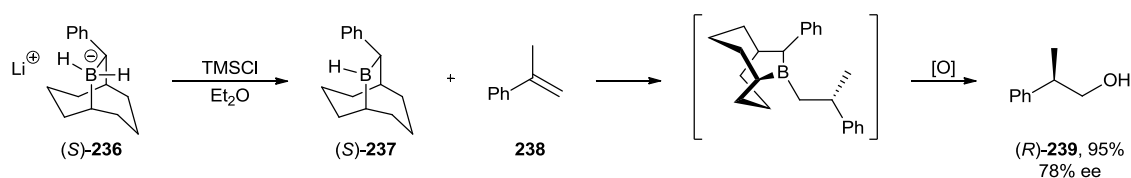
Trisubstituted alkyl olefins have also been subjected to asymmetric hydroboration, followed by oxidation, although the alcohols obtained showed only moderate

enantiopurities of 53 – 75% ee.³⁰⁸ However, superior enantioselectivities were obtained for the hydroboration of trisubstituted styrene derivatives that afforded chiral alcohol products in >80% ee (Scheme 128).³⁰⁹



Scheme 128. Asymmetric hydroboration of phenyl-substituted tertiary olefins by IpcBH_2 followed by oxidation; alcohols **235c** and **235d** were derived from (*E*)-2-phenyl-2-butene and (*Z*)-2-phenyl-2-butene, respectively.

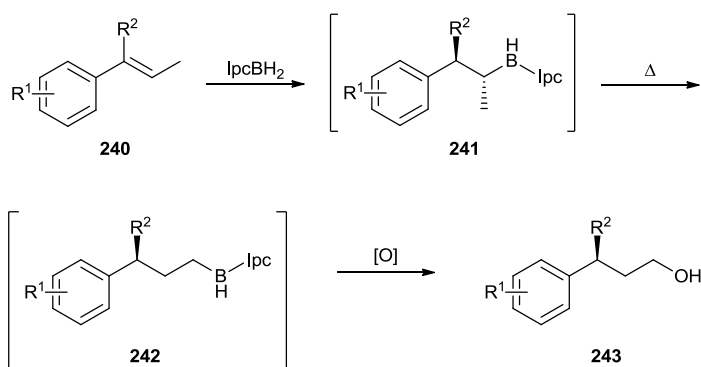
Unfortunately, neither of these conveniently accessible reagents could hydroborate 1,1'-disubstituted alkenes with a satisfactory level of enantioselectivity. To date, the highest enantioselectivities achieved for the hydroboration of this challenging substrate class have been reported by Soderquist,³¹⁰ using chiral 10-substituted 9-borabicyclo[3.3.2]decane reagents. For example, hydroboration of α -methylstyrene **238** with borane (*S*)-**237**, followed by oxidation, afforded the corresponding primary alcohol **239** in 78% ee (Scheme 129). In contrast, the equivalent reaction using IpcBH_2 resulted in the formation of alcohol **239** in just 5% ee.³¹¹



Scheme 129. Asymmetric hydroboration of α -methylstyrene.

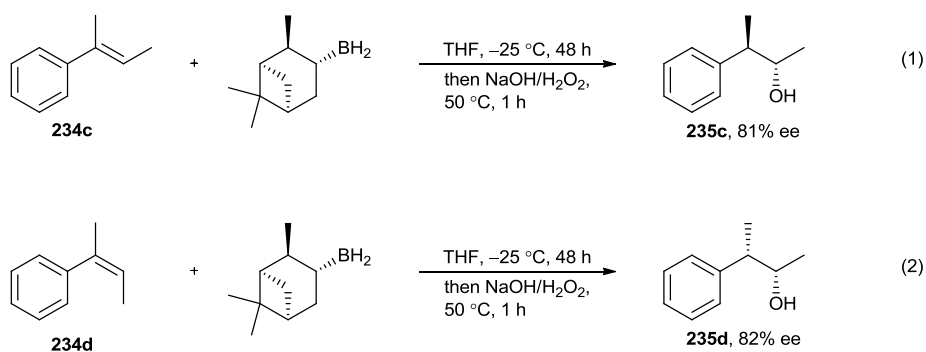
4.4 Tandem asymmetric hydroboration-isomerisation protocols

It was proposed that combining enantioselective hydroboration of a trisubstituted arylalkene with contrathermodynamic isomerisation of an internal alkene bond to a terminal position might result in a one-pot hydroboration-isomerisation-substitution sequence being developed that could furnish products containing both a benzylic stereocentre and a remote functional group. Therefore, initial treatment of substituted styrene derivative **240** with IpcBH_2 would be expected to proceed in a highly stereoselective manner to afford dialkylborane **241** (Scheme 130). This intermediate could then undergo thermal isomerisation to selectively position the boron atom at the terminus of the alkyl chain, whereupon it could be readily converted to the desired alcohol product **243**.



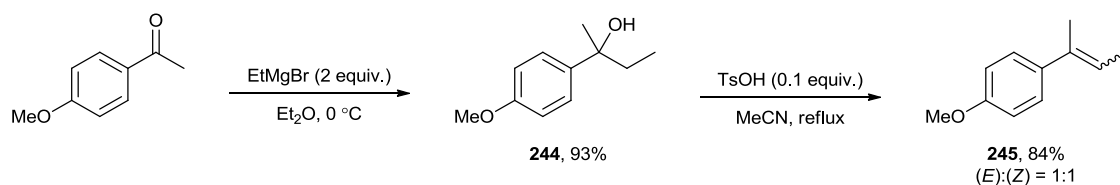
Scheme 130. Asymmetric hydroboration, followed by isomerisation for the synthesis of chiral primary alcohols containing benzylic stereocentres.

Therefore, 2-(4-methoxyphenyl)-2-butene (**245**) was chosen as a test substrate, due to the good stereoselectivities previously reported for the IpcBH_2 -mediated hydroboration-oxidation reactions of (*E*)- and (*Z*)-2-phenyl-2-butene (**234c** and **234d**, respectively, Scheme 131).³⁰⁹



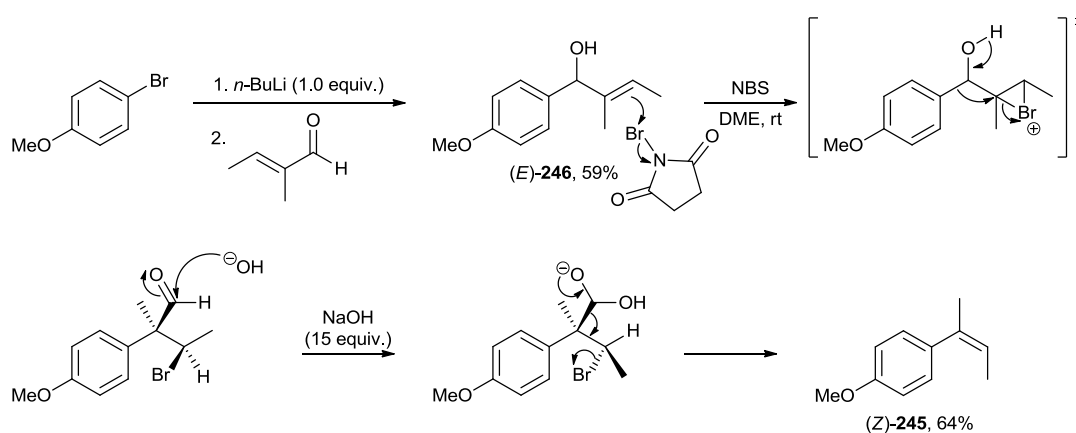
Scheme 131. Asymmetric hydroboration-oxidation of (*E*)-2-phenyl-2-butene (eq 1) and (*Z*)-2-phenyl-2-butene (eq 2) with (–)-IpcBH₂.

However, addition of 4'-methoxyacetophenone to EtMgBr, followed by acid-catalysed dehydration of tertiary alcohol **244** resulted in a chromatographically inseparable 1:1 mixture of its (*E*)- and (*Z*)-alkene isomers (Scheme 132). Therefore, a more selective preparation of geometrically pure trisubstituted arylalkenes was sought.



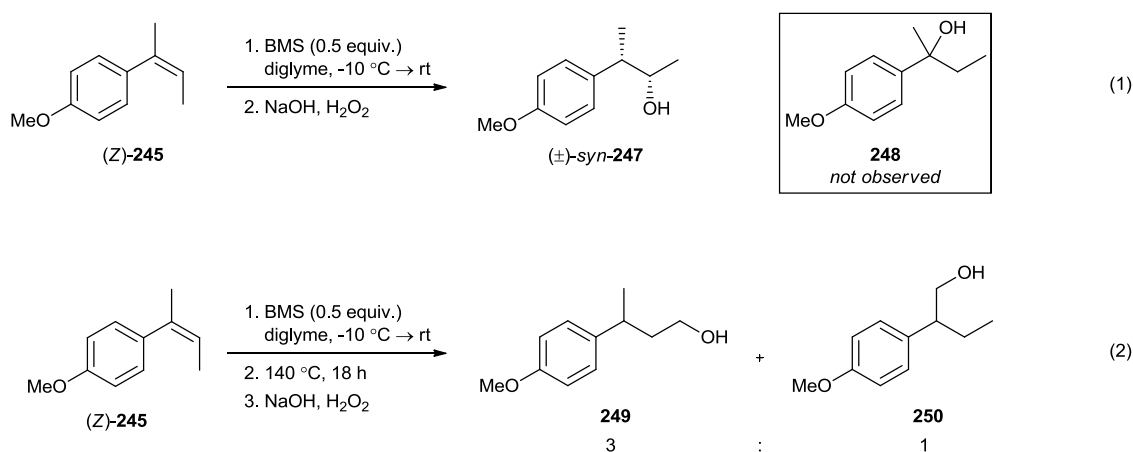
Scheme 132. Preparation of alkene **245** *via* dehydration of its tertiary alcohol precursor **244**.

To this end, allylic alcohol (*E*)-**246** was prepared *via* lithiation³¹² of 4-bromoanisole followed by addition of tiglic aldehyde. Sequential treatment of allylic alcohol (*E*)-**246** with NBS and a large excess of powdered NaOH afforded trisubstituted alkene (*Z*)-**245** (Scheme 133).³¹³ The (*Z*)-geometry of **245** was confirmed by NOE measurements that showed interactions between the alkene proton and both alkenyl methyl groups, but not between the methyl groups themselves.



Scheme 133. Preparation of alkene (Z)-245.

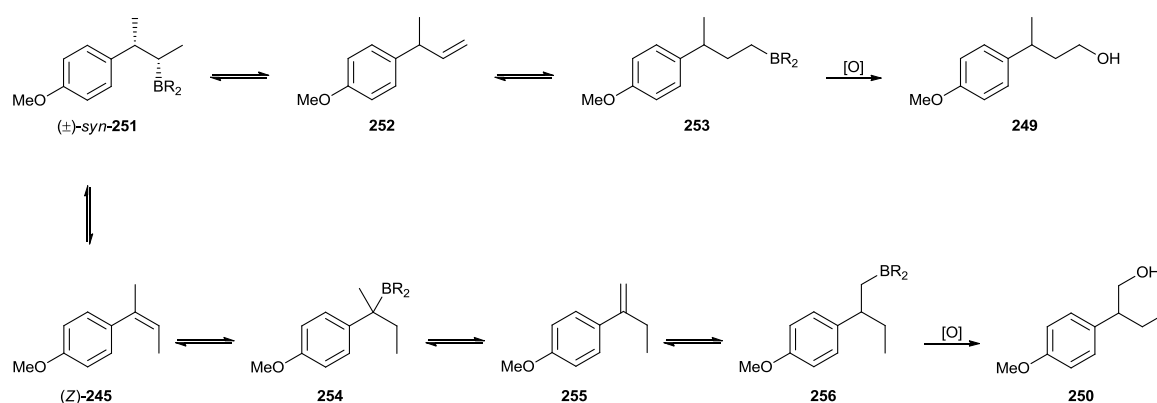
With the desired test substrate in hand, hydroboration-oxidation and hydroboration-isomerisation-oxidation reactions were carried out under standard conditions³¹⁴ using borane-dimethyl sulphide complex (BMS) in diglyme solvent, in order to obtain authentic racemic reference samples of the expected products *syn*-247 and 249 (Scheme 134, eqs 1 and 2, respectively).



Scheme 134. Hydroboration-oxidation and hydroboration-isomerisation-oxidation reactions of (Z)-245 using BMS.

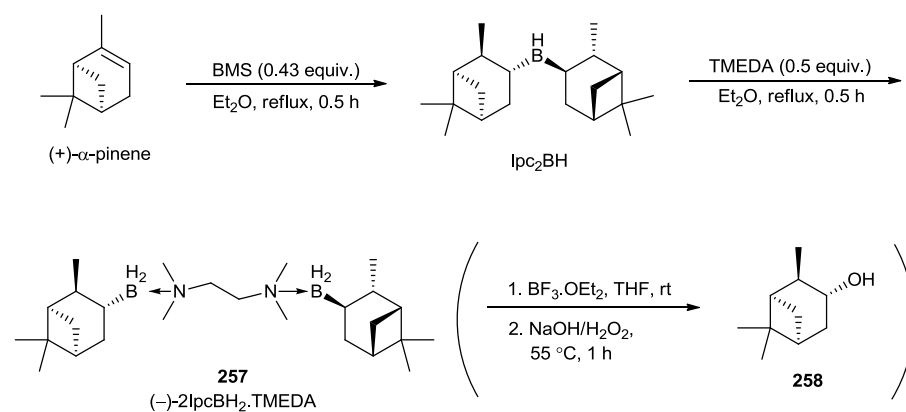
The initial hydroboration reaction proceeded with >99% regioselectivity (i.e., the alternative isomer 248 was not detected by ¹H NMR spectroscopy), affording the expected alcohol *syn*-247 upon oxidation. Heating the hydroborated intermediate at 140 °C overnight, followed by oxidation, was found to afford a mixture of two products: the desired primary alcohol 249, formed from migration of boron to the terminal position, and

an isomeric primary alcohol which was determined to be **250**. This compound presumably arises from Markovnikov-addition of borane to the starting alkene (*Z*)-**245**, followed by elimination to afford styrene **255** which is subsequently hydroborated in anti-Markovnikov fashion to form the observed primary alcohol **250** upon oxidation (Scheme 135). This was a disturbing observation since enantioselectivity would be severely compromised if such a pathway were to occur in an asymmetric hydroboration-isomerisation-oxidation reaction. However, the IpcBH_2 reagent is significantly more sterically demanding than the dialkylboranes derived from BMS and (*Z*)-**245** and it was reasoned that this might favour the desired isomerisation pathway to exclusively afford **249**.



Scheme 135. Alternative isomerisation pathways leading to primary alcohols **249** and **250**.

Following the method of Brown,³⁰⁶ the *bis*-adduct $2\text{IpcBH}_2\cdot\text{TMEDA}$ (**257**) was synthesised from commercially available (+)- α -pinene (Scheme 136). However, the ^1H and ^{11}B NMR spectra of the product obtained were not in agreement with the published data, although the product was found to afford the known isopinocampheol **258** upon oxidation with alkaline hydrogen peroxide. Consequently, an X-ray crystal structure of the product was acquired which confirmed its structure (Figure 9), whilst analysis of a commercially available sample (Sigma Aldrich) showed identical ^1H and ^{13}C NMR spectra and also the same value of specific rotation.



Scheme 136. Synthesis of 2IpcBH₂.TMEDA (**257**) from (+)- α -pinene.

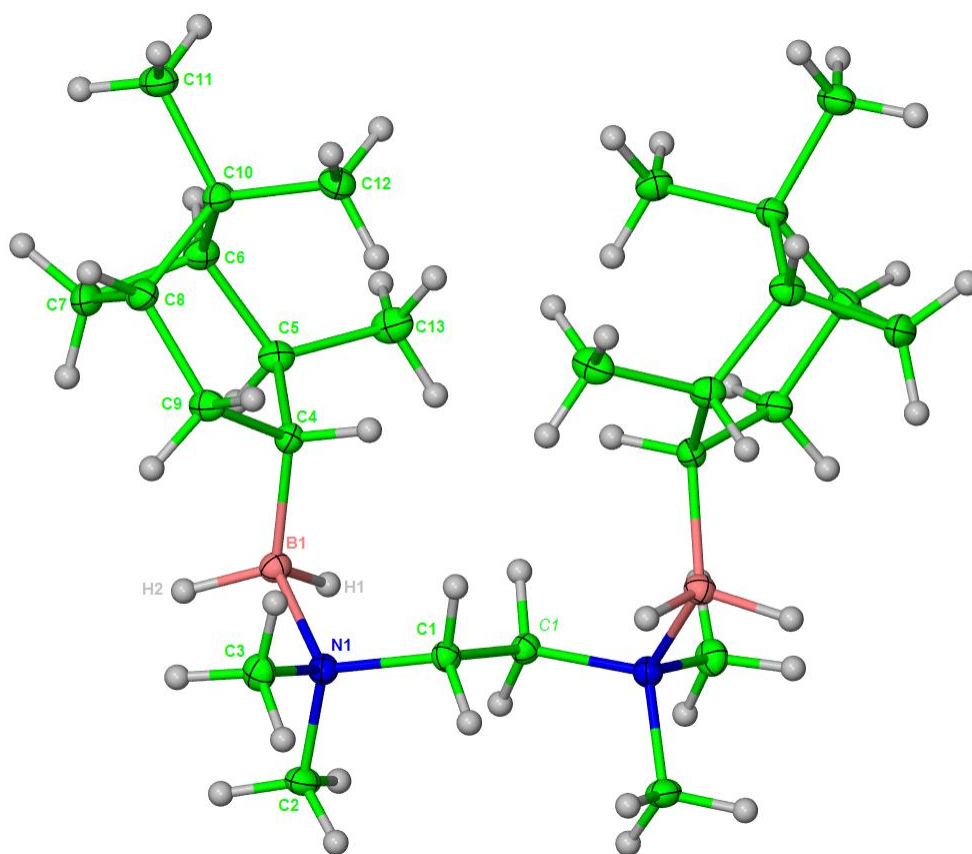
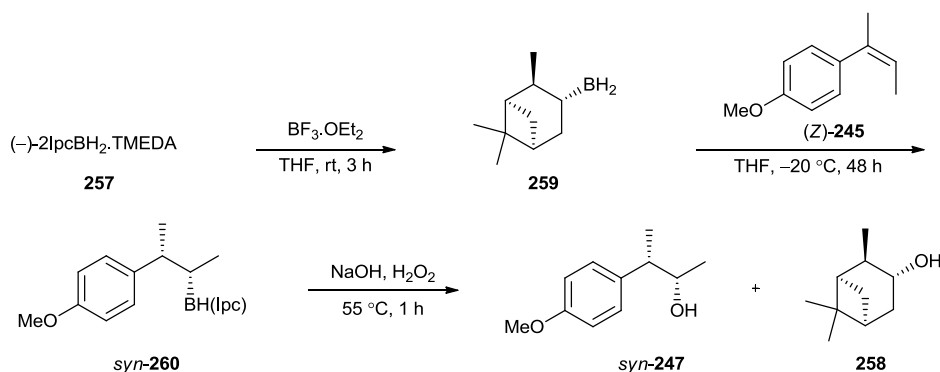


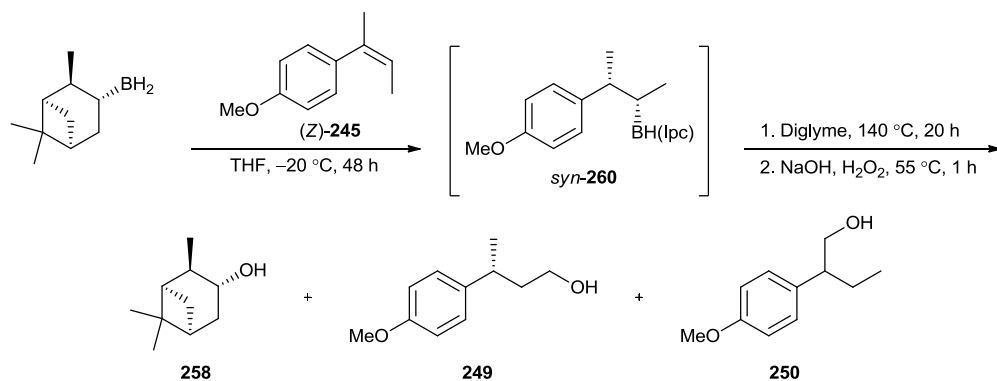
Figure 9. X-Ray crystal structure of *bis*-monoisopinocampheylborane TMEDA complex (2IpcBH₂.TMEDA, **257**), synthesised from (+)- α -pinene.

The initial asymmetric hydroboration reaction was carried out as follows: (–)-monoisopinocampheylborane (**259**) was liberated from its TMEDA adduct, (–)-2IpcBH₂.TMEDA (**257**), via treatment of its THF solution with BF₃.OEt₂ (Scheme 137).³¹⁵ Oxidation of the dialkylborane intermediate using alkaline hydrogen peroxide solution gave alcohol **247**, which was purified by column chromatography and the enantiomeric excess (ee) determined to be >99% by chiral HPLC over an OD-H stationary phase.



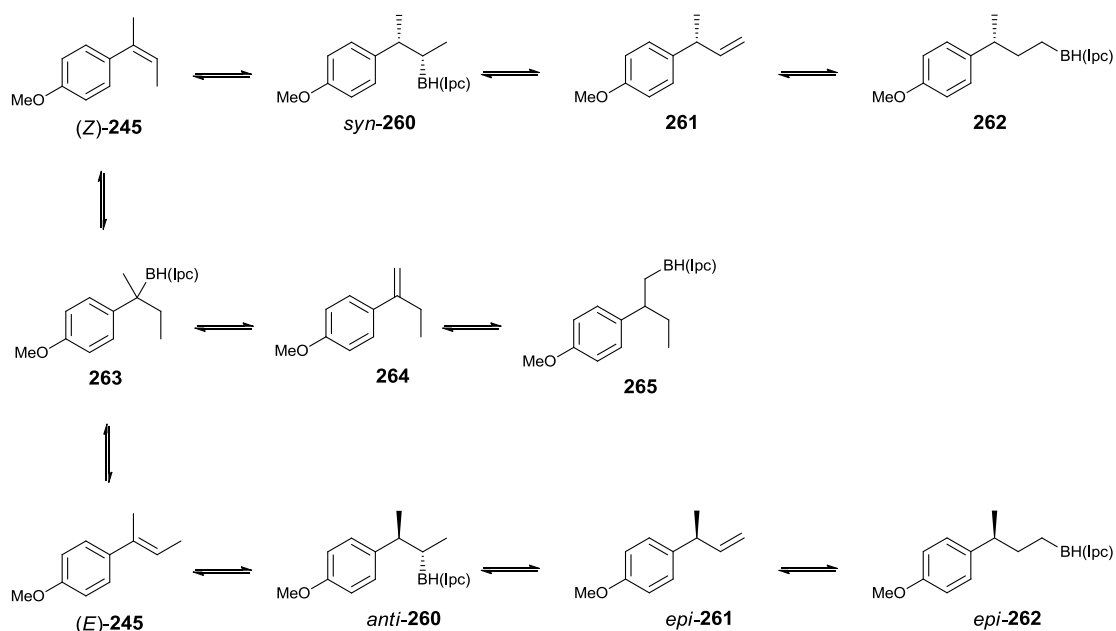
Scheme 137. Asymmetric hydroboration of alkene (Z)-245.

The hydroboration-isomerisation-oxidation sequence was carried out in an analogous manner (Scheme 138). Upon completion of the asymmetric hydroboration step, a small aliquot was removed and worked up as described above in order to verify the enantioselectivity of this step (>99% ee). The remaining reaction mixture was then subjected to isomerisation conditions involving replacement of the THF solvent with diglyme, heating at 140 °C for 20 hours and subsequent oxidation with alkaline hydrogen peroxide. Three products were isolated *via* column chromatography: isopinocampheol (**258**) and the primary alcohols **249** and **250**. Sadly, the ee of alcohol **249** was found to be only 5% *via* chiral HPLC analysis.



Scheme 138. Asymmetric hydroboration-isomerisation-oxidation of alkene (Z)-245.

Therefore, it appears that the high reaction temperature required for the migration pathway to occur has resulted in the boron reagent undergoing migration along the length of the alkyl chain to afford essentially racemic product **249** under thermodynamic control. The isolation of primary alcohols **249** and **250**, combined with the absence of any tertiary alcohol arising from oxidation of the intermediate organoborane **263** or any alkene-containing species **261/264**, confirms that the boron reagent preferentially resides at the two ends of the alkyl chain (Scheme 139). Therefore, all other species are short-lived intermediates which are present in vanishingly small concentrations at any given time. The rapid reversible addition of IpcBH_2 to styrene (*Z*)-**245** at 140 °C clearly provides a facile pathway to a racemic product under thermodynamic control. Furthermore, the isolation of alcohol **250** from this reaction clearly indicates that a tertiary organoborane species **263** must also be reversibly formed under these conditions. This tertiary borane species can potentially eliminate to form two different trisubstituted alkenes, (*E*)-**245** and (*Z*)-**245**, which in turn would then be hydroborated, isomerised and oxidised to afford opposing enantiomers of the primary alcohol **249**.



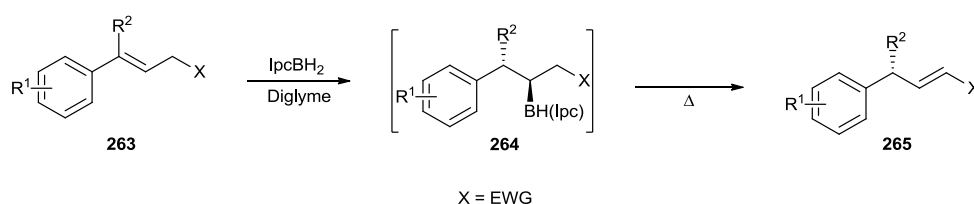
Scheme 139. Asymmetric hydroboration of alkene (*Z*)-**245**, followed by isomerisation and racemisation.

In an attempt to develop more stereoselective conditions, it was then decided to monitor the enantiomeric purity of alcohol **249** and the product distribution of the hydroboration-isomerisation reaction over time. Unfortunately, it was found that the ee of the small

amount of primary alcohol **249** produced was just 8% after one hour at 140 °C, with an essentially identical 3:1 ratio of the primary alcohols **249** and **250** being present. It was concluded that the use of this type of hydroboration-isomerisation protocol for the asymmetric synthesis of chiral alcohols containing β -stereocentres was not viable.

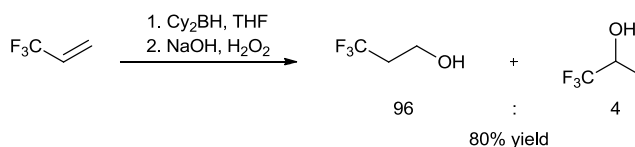
4.5 Hydroboration of β,γ -unsaturated esters

As the unselective nature of the organoborane isomerisation process to afford styrene **245** was an inherent problem, rather than the level of asymmetric induction in the initial hydroboration step, the substrate was re-designed in an attempt to preserve the benzylic stereocentre of the product. It was reasoned that if the initial elimination step of an intermediate organoborane species **264** would afford a thermodynamically more stable alkene that was less susceptible to reaction with the borane reagent, then the stereochemical integrity of the benzylic centre might be retained (Scheme 140).



Scheme 140. Asymmetric hydroboration and isomerisation of a suitably functionalised trisubstituted arylalkene.

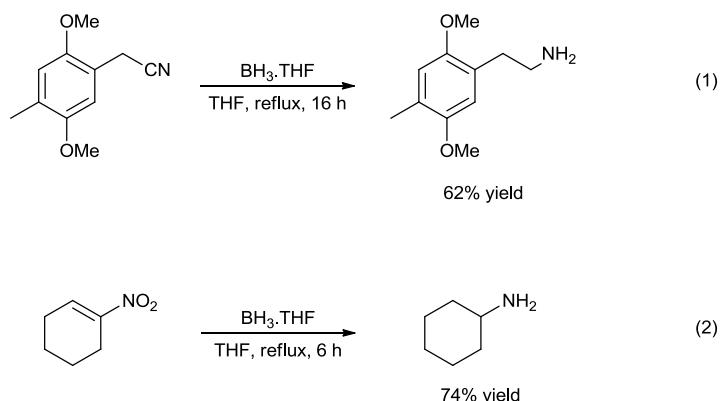
Our initial thoughts were that an alkene conjugated to a suitable electron withdrawing group *could* constitute a thermodynamic trap by withdrawing electron density from the isomerised alkene bond of **265**, thus rendering it essentially unreactive toward hydroboration. A review of the literature revealed that electron-deficient alkenes such as 3,3,3-trifluoropropene could readily undergo hydroboration reactions (Scheme 141).³¹⁶



Scheme 141. Hydroboration of an electron-deficient alkene.

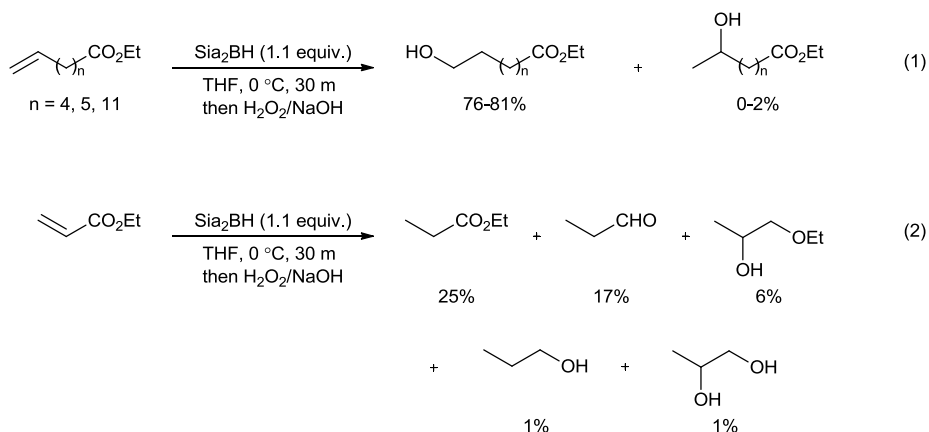
Alternative electron-withdrawing groups such as cyano or nitro that would disfavour hydroboration and confer synthetic versatility to the product were deemed unsuitable due

to their potential to undergo competing borane-mediated reduction pathways to afford primary amines (Scheme 142, eqs 1 and 2).^{317,318}



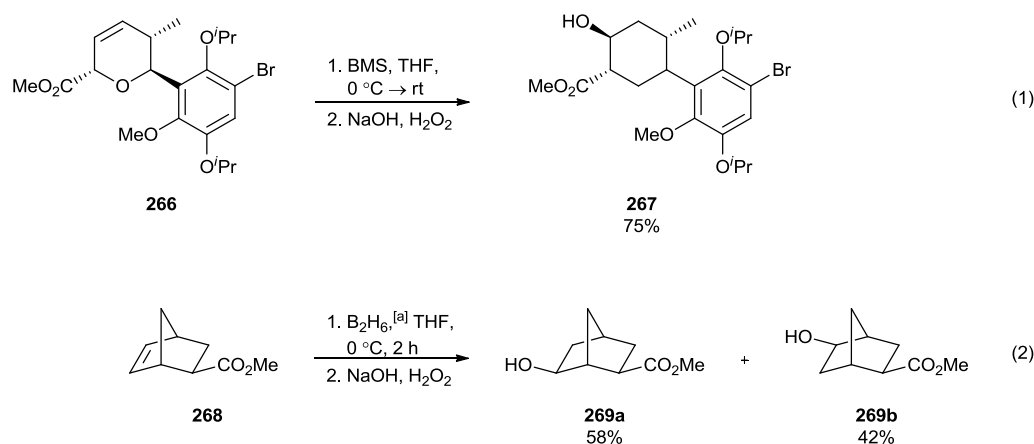
Scheme 142. Borane-mediated reduction of cyano and α,β -unsaturated nitroalkene groups.

However, borane-mediated reduction of the alkene substituents of α,β -unsaturated ester derivatives does not generally occur, therefore we considered using a strategy based on the reversible hydroboration of β,γ -unsaturated esters. Brown's original investigations into the hydroboration reactions of unsaturated esters to afford their corresponding hydroxy esters appeared promising.^{319,320} In summary, addition of $\text{BH}_3\cdot\text{THF}$ to ethyl 3-butenolate, 4-pentenoate and 10-undecenoate esters followed by oxidative work-up gave their corresponding ω -hydroxy esters, with small amounts of secondary hydroxy ester and diol by-products also being isolated. Utilisation of the bulkier disiamylborane (Sia_2BH) further increased the regioselectivity and, notably, did not result in any reduction of the ester functionality (Scheme 143, eq 1). However, in both cases attempted hydroboration of ethyl acrylate was found to afford a complex mixture of products (Scheme 143, eq 2), with essentially no β -hydroxy ester being produced.



Scheme 143. Selective hydroboration of unsaturated esters to afford their corresponding ω -hydroxy esters (eq 1) and the anomalous reactivity of ethyl acrylate under hydroboration conditions (eq 2).

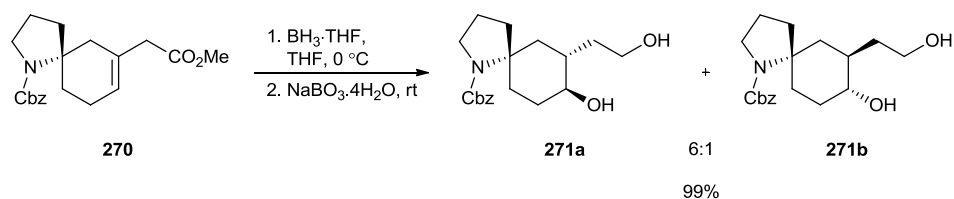
However, a few literature reports describing chemoselective hydroboration of β,γ -unsaturated esters, without concomitant reduction of the ester were known.³²¹ For example, hydroboration of dihydropyran **266** (Scheme 144, eq 1)³²² under standard conditions gave the desired β -hydroxy ester **267** in good yield upon oxidative work-up, whilst hydroboration of the norbornenyl ester **268** (Scheme 144, eq 2)³²³ with diborane afforded a mixture of β - and γ -hydroxy esters **269a/269b** in good yield.



Scheme 144. Hydroboration reactions of β,γ -unsaturated esters.

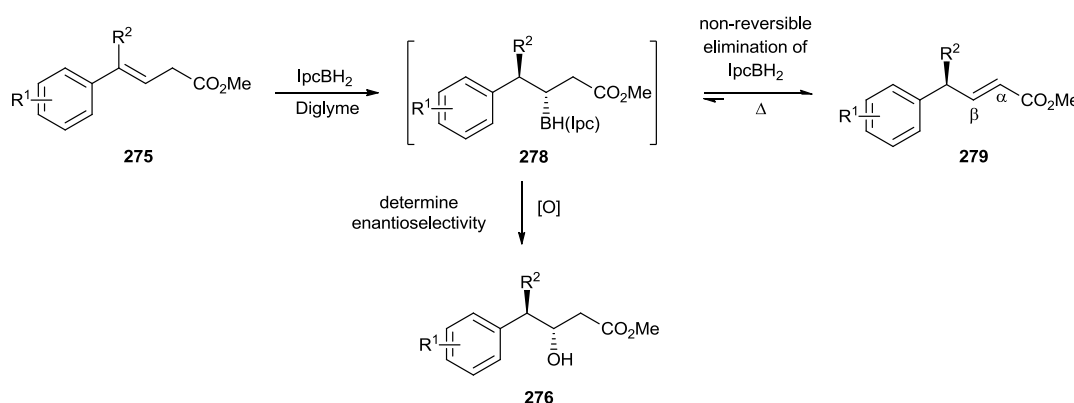
[a] Generated externally from addition of NaBH_4 to $\text{BF}_3 \cdot \text{OEt}_2$ in DME.

However, during the course of their synthesis of the natural product FR901483, Martin and co-workers³²⁴ reacted β,γ -unsaturated ester **270** with a variety of borane reagents (BMS , ThxBH_2 , Cy_2BH , 9-BBN) and obtained a diastereomeric mixture of diol products **271a/271b** upon oxidative work-up (Scheme 145). Even the utilisation of the corresponding carboxylate acid salt of **270** did not prevent reduction of the carbonyl group.



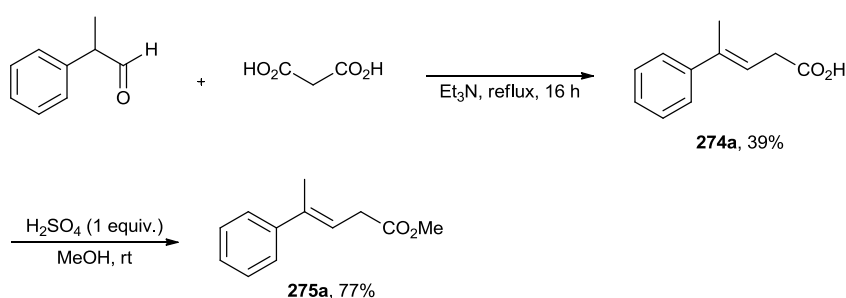
Scheme 145. Hydroboration of a β,γ -unsaturated ester with undesired ester reduction.

It was therefore anticipated that, in the absence of competing/concomitant ester reduction, hydroboration of β,γ -unsaturated ester **275** would afford an intermediate organoborane **278**, the enantiopurity of which could be readily verified following its oxidation to chiral β -hydroxy ester **276** (Scheme 146). Upon heating, isomerisation of **278** would occur to afford its corresponding α,β -unsaturated isomer **279**, that would be unreactive towards the hydroborating agent and thus potentially block the isomerisation/racemisation pathway discussed previously.



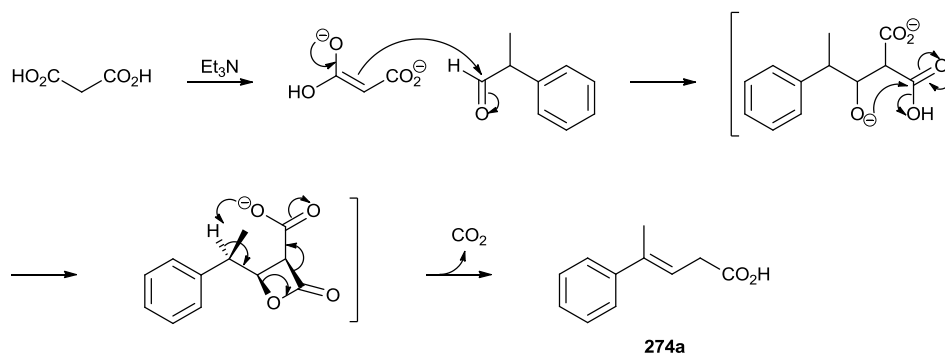
Scheme 146. Planned sequence of asymmetric hydroboration-isomerisation to afford γ -chiral α,β -unsaturated esters **279**.

The simple β,γ -unsaturated ester **275a** was subsequently chosen as a test substrate and prepared *via* a literature route involving a Knoevenagel reaction between the enolate of malonic acid and 2-phenylpropionaldehyde which directly gave β,γ -unsaturated acid **274a**,³²⁵ that was then subjected to a straightforward Fischer esterification reaction with methanol (Scheme 147).



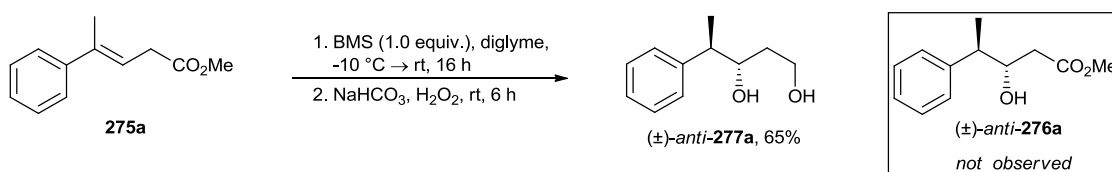
Scheme 147. Synthesis of β,γ -unsaturated ester **275a** *via* Knoevenagel reaction of 2-phenylpropionaldehyde.

The mechanism of this reaction was not discussed in the original paper, however it is proposed that the exclusive formation of the β,γ -unsaturated isomer, and the high (*E*)-selectivity observed, can be explained by the following mechanism (Scheme 148). Aldol reaction of a malonate enolate equivalent with 2-phenylpropionaldehyde affords an aldol product that ring closes to afford a β -lactone which then eliminates CO_2 from a cyclic transition state. This cyclic transition state positions its methyl group *anti* to the β -lactone group thus favouring formation of an (*E*)-alkene.



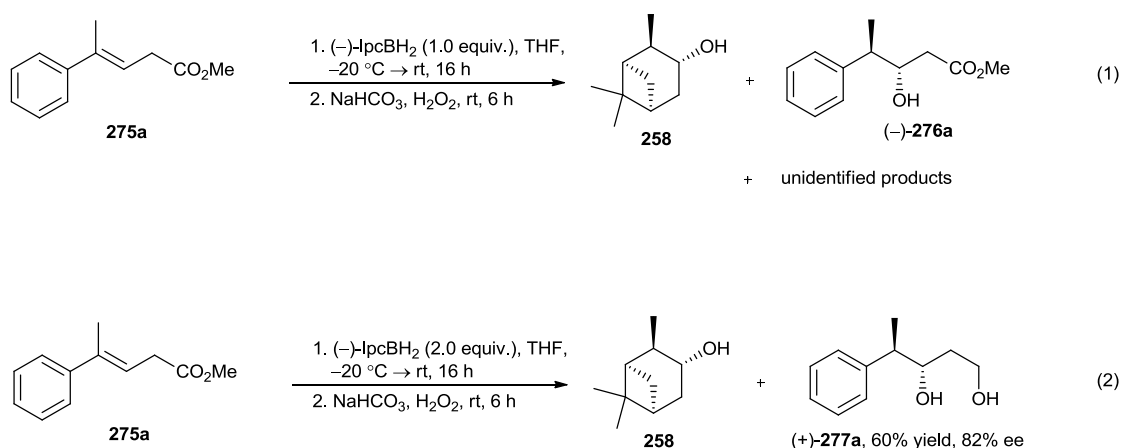
Scheme 148. Proposed mechanism of the Knoevenagel reaction between malonic acid and 2-phenylpropionaldehyde to afford β,γ -unsaturated carboxylic acid **274a**

The β,γ -unsaturated ester **275a** was subsequently treated with BMS in diglyme, over a period of 16 hours, and the reaction mixture oxidised under mild conditions ($\text{H}_2\text{O}_2/\text{NaHCO}_{3(\text{aq})}$ to avoid hydrolysis of the ester).³²⁶ Diglyme was removed from the reaction mixture by dilution with ether and washing with water, and the crude product analysed directly (Scheme 149). The ^1H and ^{13}C NMR spectra from this reaction revealed the presence of one compound, containing no resonances corresponding to the presence of a methoxy group. Upon closer inspection it was clear that diol **277a** had been formed *via* hydroboration and a concomitant reduction of the ester group of **275a**, with none of the expected *anti*- β -hydroxy ester **276a** being present.



Scheme 149. Attempted hydroboration-oxidation of β,γ -unsaturated ester **275a** with BMS.

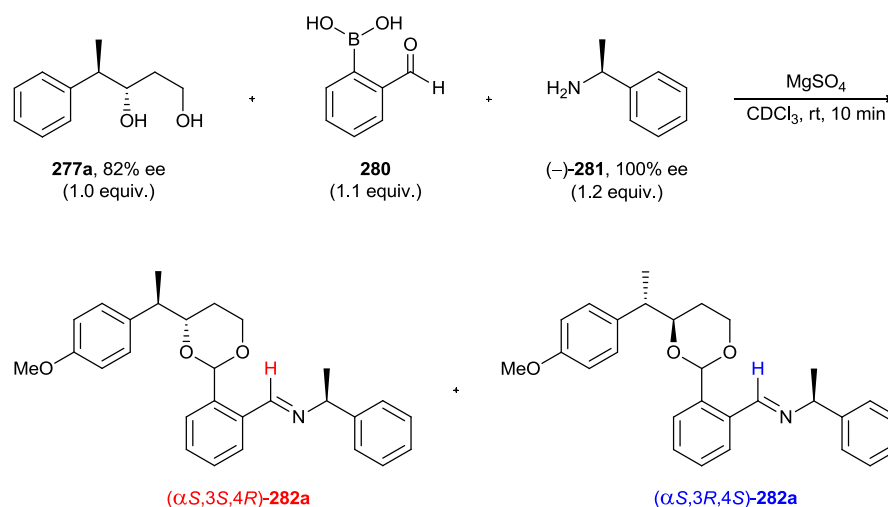
This result clearly implied that it was going to be difficult to carry out our proposed hydroboration/isomerisation protocol on this class of substrate. However, there is currently much interest in developing tandem synthetic protocols in which two or more transformations occur consecutively in a single reaction vessel. Consequently, it was decided to determine the scope and limitation of this reaction for the one-pot asymmetric synthesis of new types of chiral diols containing γ -stereocentres. Therefore, ester **275a** was reacted with both one and two equivalents of (–)-IpcBH₂ and oxidised under the same mild conditions (H₂O₂/NaHCO_{3(aq)}). Treatment of **275a** with one equivalent of the chiral borane resulted in the formation of a ~1:1 mixture of the original, unreacted ester **275a** and β -hydroxy ester **276a**, with isopinocampheol **258** and minor amounts of unidentified products also present (Scheme 150, eq 1). When two equivalents of chiral borane were used, the hydroboration reaction proceeded to completion with complete reduction of the ester group to afford diol **277a** and isopinocampheol **258** upon oxidation (Scheme 150, eq 2).



Scheme 150. Treatment of ester **275a** with one (eq 1) or two (eq 2) equivalents of (–)-IpcBH₂ results in different mixtures of products.

Following isolation, the enantiomeric excess of (+)-**277a** was determined to be 82% by a ¹H NMR chiral derivatisation method previously reported by the Bull and James groups.³²⁷ Therefore, two samples of chiral diol **277a** were treated with (2-formyl)phenylboronic acid **280** and either racemic or enantiopure α -methylbenzylamine **281** in CDCl₃. The use of racemic amine served as a control, whilst the chiral diol treated with enantiopure amine results in formation of a pair of diastereomeric imine derivatives (*R,S,S*)-**282a** and (*S,R,S*)-

282a (Scheme 151). The ratio of these two species, determined by integration of the imine resonances in their 500 MHz ^1H NMR spectrum (Figure 10b), is a direct reflection of the enantiopurity of the parent chiral diol **277a**.³³²



Scheme 151. Derivatisation protocol for determination of enantiopurity of diol **277a**.

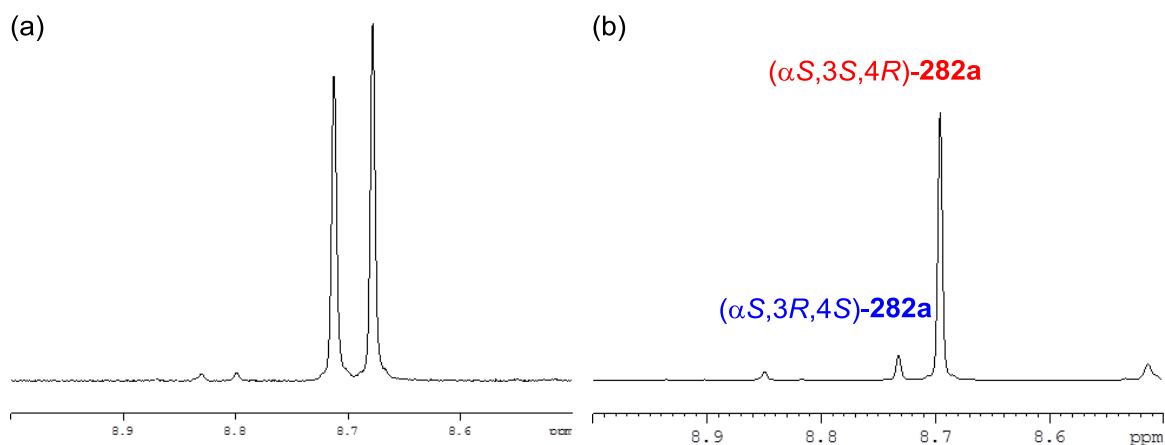
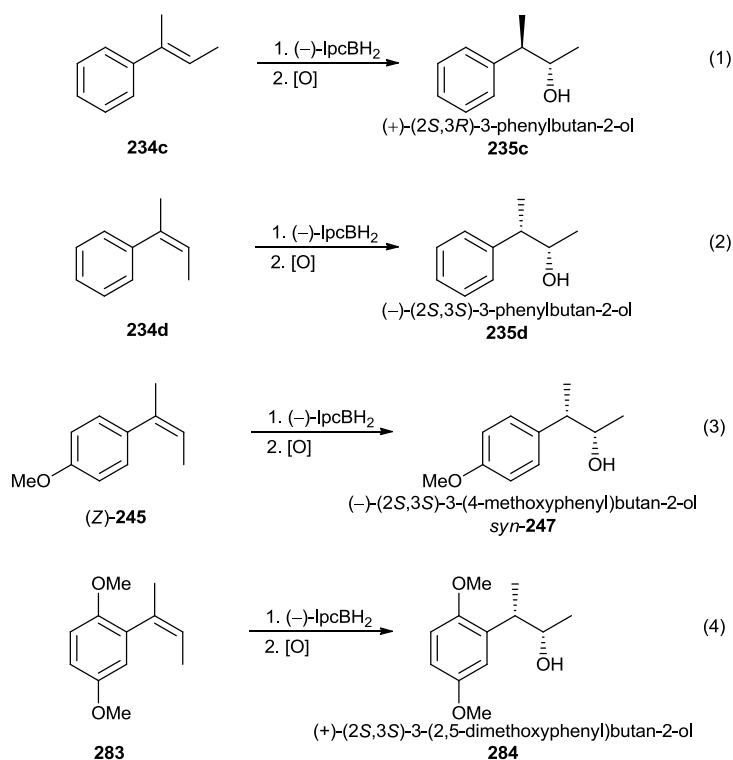


Figure 10. ^1H NMR spectra showing diagnostic signals corresponding to the imine resonances of the diastereoisomeric derivatives $(S,R,S)/(S,S,R)\text{-282a}$ using (a) racemic α -methylbenzylamine $(\pm)\text{-281}$, and (b) enantiopure $(S)\text{-}\alpha$ -methylbenzylamine $(-)\text{-281}$.

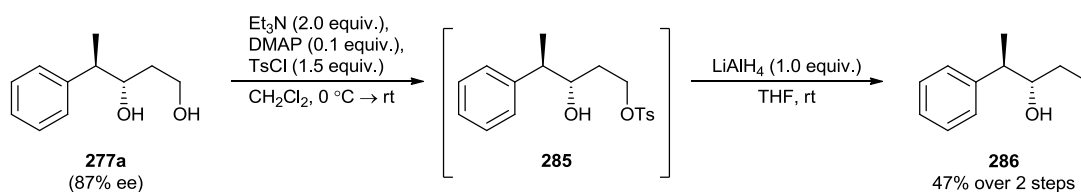
4.6 Assignment of stereochemistry

Unfortunately, diol **277a** was a novel compound and so its configuration could not be assigned directly from the sign of its specific rotation. However, its configuration could be implied from the products obtained by Brown from the hydroboration-oxidation reactions of (*E*)- and (*Z*)-2-phenyl-2-butene (Scheme 152, eqs 1 and 2, respectively).³¹⁶ When I performed an equivalent reaction using (*Z*)-3-(4-methoxyphenyl)-2-butene (**245**) and (–)-IpcBH₂ of known absolute configuration, the product alcohol also displayed a negative value for its specific rotation (Scheme 152, eq 3). Substitution of the aromatic rings of analogous compounds with a 4-methoxyl substituent has not been observed to alter the sign of rotation (see Experimental Section, compounds **277a** and **277c**). Furthermore, the results of Nichols and co-workers,³²⁸ whose assignment of both the absolute stereochemistry of product alcohol **284** and configuration of borane reagent were unambiguous, also correlate with these conclusions (Scheme 152, eq 4). Based upon these results, the stereochemical course for hydroboration reactions of (*E*)- or (*Z*)-trisubstituted arylalkenes using (–)-IpcBH₂ can be reliably predicted.



Scheme 152. Stereochemical course of the asymmetric hydroboration of (*E*)- and (*Z*)-trisubstituted alkenes with (–)-IpcBH₂.

However, the presence of the potentially coordinating ester group in **275a** could alter the enantiofacial selectivity of the hydroboration step. Therefore, the configuration of diol **277a** was established *via* its conversion to mono-tosylate **285**, followed by reduction with LiAlH₄ to secondary alcohol **286** (Scheme 153). The sign of the specific rotation of **286** derived from diol **277a** was found to be positive, whereas the literature value for the specific rotation of (2*R*,3*S*)-2-phenyl-3-pentanol (i.e. (–)-**286**) is negative (Figure 11).³²⁹ This confirmed that diol **277a** possessed the absolute stereochemistry which was predicted by comparison with products of known absolute configuration from previously reported asymmetric hydroboration reactions of simple (*E*)-trisubstituted alkenes (Scheme 152, eqs 1, 2 and 4).



Scheme 153. Conversion of diol **277a** into the known alcohol **286** in order to determine its absolute configuration.

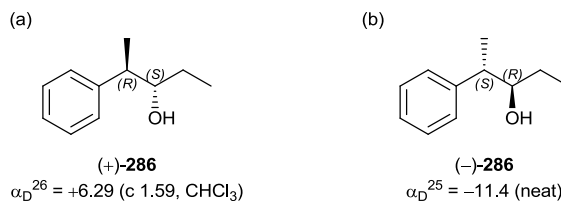
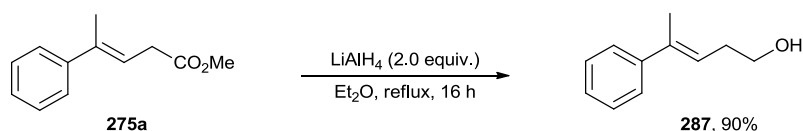


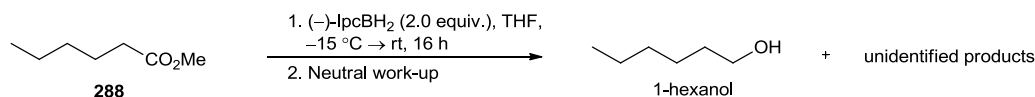
Figure 11. Specific rotation and stereochemical assignments of 2-phenyl-3-pentanol (a) derived from diol **277a**, (b) literature value.

Reaction of ester **275a** with a single equivalent of (–)-IpcBH₂ did not result in the formation of any unsaturated alcohol **287**, which implies that hydroboration of the alkene occurs considerably faster than reduction of the ester under these conditions, in agreement with Brown's results.³²⁰ This was confirmed by carrying out an independent synthesis of allylic alcohol **287** *via* reduction of ester **275a** with LiAlH₄ in ether (Scheme 154), that enabled us to determine it was not present in the ¹H NMR spectrum of the crude hydroboration reaction mixture.



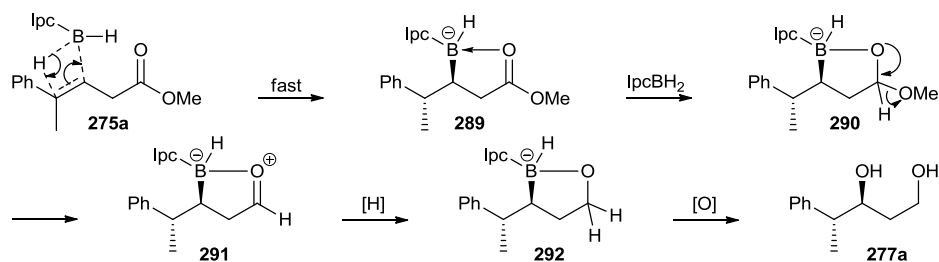
Scheme 154. Synthesis of an authentic sample of alcohol **287**.

The fact that no reduction of the ester functionality is observed when one equivalent of borane was employed in the hydroboration reaction implies that a second equivalent of borane is likely to participate in the ester reduction step, with a hydride equivalent being potentially delivered in an intramolecular fashion. In order to ascertain whether the presence of an “internal” borane substituent is required to activate the ester, the saturated aliphatic ester methyl hexanoate **288** was reacted with two equivalents of (–)-IpcBH₂, under otherwise identical conditions, resulting in complete consumption of starting material and formation of 1-hexanol (Scheme 155). This implies that (–)-IpcBH₂ is indeed capable of reducing an isolated ester group to its corresponding alcohol when present in excess and does not depend upon an alkene moiety being present in the substrate.



Scheme 155. Reduction of a saturated ester with (–)-IpcBH₂.

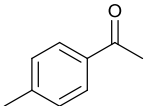
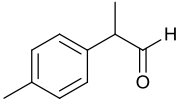
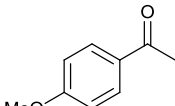
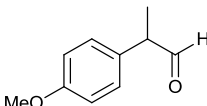
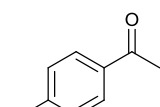
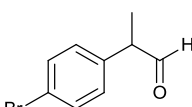
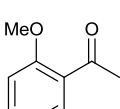
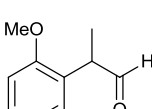
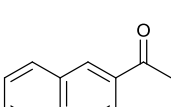
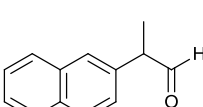
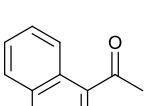
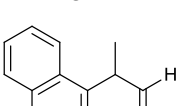
A plausible mechanism for the reduction of **275a** is as follows (Scheme 156): addition of (–)-IpcBH₂ to the alkene bond of **275a** affords organoborane **289**; intramolecular coordination of the ester’s acyl oxygen to boron increases the electrophilicity of the carbonyl carbon atom and facilitates hydride addition by a second molecule of (–)-IpcBH₂ to afford intermediate **290**; the methoxy group then leaves to afford an oxonium species **291** that is further reduced to afford organoborane **292**, which affords diol **277a** upon oxidation.



Scheme 156. Proposed mechanism of the hydroboration-reduction of ester **275a** by (–)-IpcBH₂.

In order to establish the general applicability of this reaction, a series of analogues with different substituents in their aromatic ring were prepared. In contrast to 2-arylpropionaldehydes, a large number of substituted acetophenones are commercially available, allowing rapid access to the desired aldehydes via a two-step Wittig C₁-homologation/enol ether hydrolysis protocol.^{330,331} In all cases, hydrolysis of the enol ether intermediates proceeded readily and the aldehydes **273b-g** were isolated in unoptimised overall yields of approximately 50% (Table 30).

Table 30. Synthesis of 2-arylpropionaldehydes from their corresponding acetophenones/acetonaphthones.

$ \begin{array}{c} \text{Ar}-\text{C}(=\text{O})\text{CH}_3 \\ \text{272b-g} \end{array} \xrightarrow[\text{THF, 0 } ^\circ\text{C, 15 m; rt, 16 h}]{[\text{MeOCH}_2\text{PPh}_3]^+\text{Br}^-, \text{BuLi}} \left[\text{Ar}-\text{C}(\text{OMe})=\text{CHCH}_3 \right] \xrightarrow[\text{THF, reflux, 3 h}]{\text{conc. HCl}} \begin{array}{c} \text{Ar}-\text{CH}(\text{CH}_3)\text{CHO} \\ \text{273b-g} \end{array} $			
Entry	Ketone (272)	Aldehyde (273)	Isolated yield
1	 272b	 273b	60%
2	 272c	 273c	52%
3	 272d	 273d	60%
4	 272e	 273e	48%
5	 272f	 273f	55%
6	 272g	 273g	40%

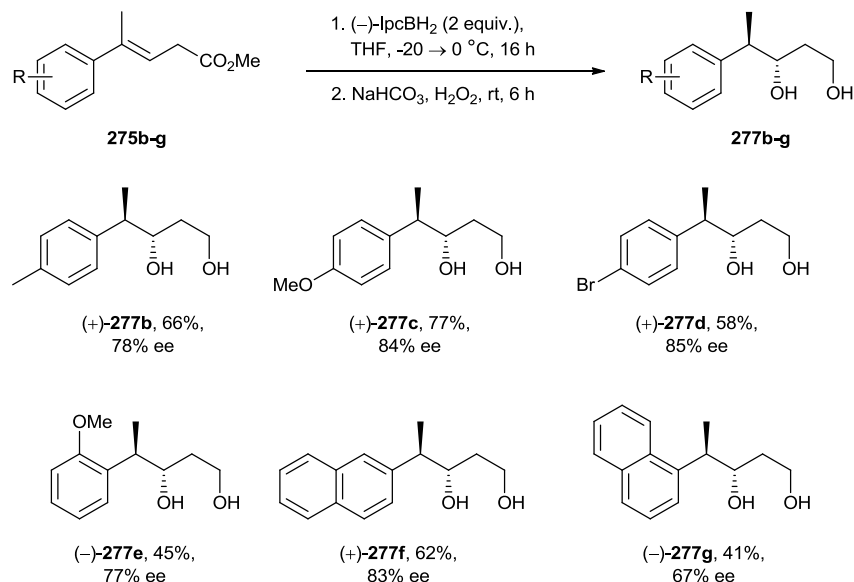
All six aldehydes **273b-g** were then reacted with malonic acid under the previously utilised Knoevenagel reaction conditions³²⁵ to afford their corresponding β,γ -unsaturated carboxylic acids **274b-g**. Although the acids were formed as mixtures of (*E*)- and (*Z*)-isomers, the (*E*):(*Z*) ratios were generally high. The subsequent esterification reactions then proceeded readily to afford, after chromatographic purification, five geometrically pure (*E*)- β,γ -unsaturated esters **275b-f** (Table 31). Unfortunately, the geometric isomers of the 1-naphthyl substituted ester **275g** could not be completely separated.

Table 31. Synthesis of β,γ -unsaturated carboxylic acid esters *via* Knoevenagel reactions between malonic acid and 2-arylpropionaldehydes, followed by Fisher esterification reactions.

Entry	3-Arylpropionaldehyde (273)	4-Arylpent-3-enoic acid (274) isolated yield, (<i>E</i>):(<i>Z</i>)	Methyl (<i>E</i>)-4-arylpent-3-enoate (275), isolated yield
1	 273b	 274b , 43%, 10:1	 275b , 79%
2	 273c	 274c , 34%, 10:1	 275c , 83%
3	 273d	 274d , 33%, 7:1	 275d , 80%
4	 273e	 274e , 35%, 5:1	 275e , 56%
5	 273f	 274f , 46%, 8:1	 275f , 74%
6	 273g	 274g , 34%, 4:1	 275g , 35% ^[a]

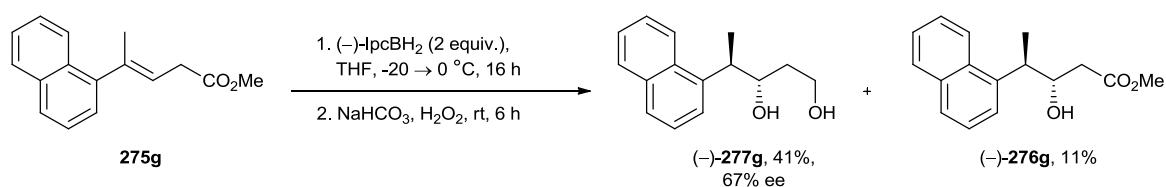
[a] Methyl ester **275g** was isolated as a mixture of alkene geometric isomers, (*E*):(*Z*) = 4:1.

Under the standard hydroboration reaction conditions using two equivalents of (–)-IpcBH₂ in THF at –20 to 0 °C, over 16 hours, each ester was hydroborated-reduced, followed by oxidation with NaHCO₃/H₂O₂ to afford their corresponding chiral diols (Scheme 157). The enantiomeric excess of these diols was determined by NMR as described previously for the parent diol **277a** *via* derivatisation of two separate samples with 2-formyl-phenylboronic acid **280** and either enantiopure or racemic α -methylbenzylamine ((–)-**281** or (±)-**281**, respectively).



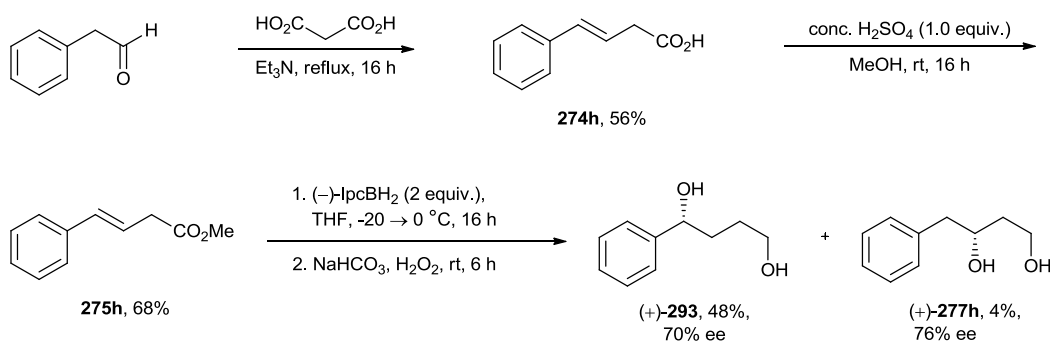
Scheme 157. Asymmetric hydroboration of β,γ -unsaturated esters **275b-g** to afford chiral diols **277b-g**.

The chiral diols **277b-g** were obtained in generally good 67–85% ee's, implying that the electronic nature of the aryl substituents did not appear to adversely affect the levels of enantioselectivity. However, ester **275e**, which is substituted in the 2-position relative to the alkenyl substituent, afforded its respective diol **277e** in a slightly lower 77% ee. The lowest ee was observed for the 1-naphthyl substituted ester **275g**, which could be due to the smaller difference in steric environments between the enantiotopic faces of the alkene. Indeed, this was also the only substrate which was found to afford a detectable quantity of its corresponding β -hydroxy ester product (**276g**, Scheme 158).



Scheme 158. Hydroboration of ester **275g** with (–)-IpcBH₂ affords a mixture of diol and β-hydroxy ester.

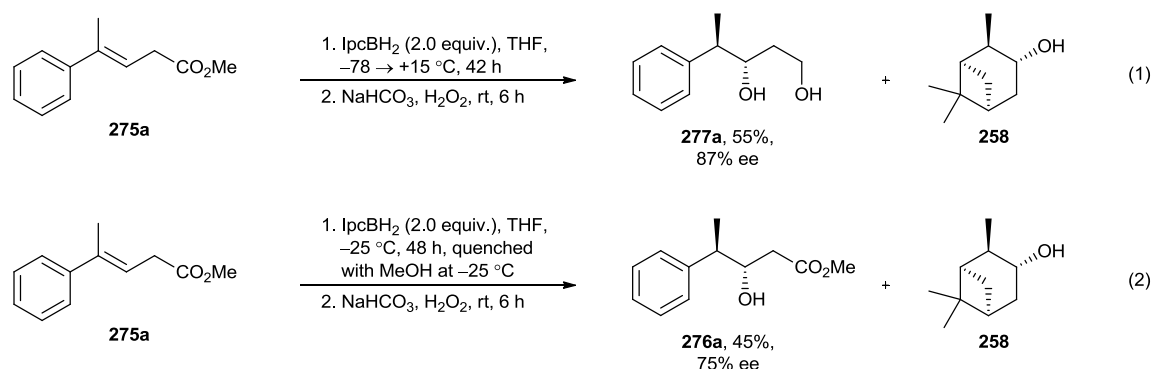
Lastly, the disubstituted β,γ-unsaturated ester **275h** was synthesised from phenylacetaldehyde using our standard Knoevenagel conditions (Scheme 159). Hydroboration of **275h** under our standard conditions proceeded with poor regioselectivity, affording a 10:1 mixture of 1-phenyl-1,4-butanediol **293** and the expected 1,3-diol **277h**. The enantiomeric excesses of these diols were again determined by NMR as described previously for the parent diol **277a** and found to be 70% for **293** and 76% for the minor isomer **277h**. The stereochemical assignments are based upon comparison to the literature values reported for these two diols and are consistent with the facial selectivity previously observed with the (–)-IpcBH₂ reagent. Although the reduced enantioselectivity was expected and is clearly due to the lower steric demand of the disubstituted alkene bond, the reversal of regioselectivity was not anticipated.



Scheme 159. Synthesis and asymmetric hydroboration with (–)-IpcBH₂ of a β,γ-unsaturated ester featuring a disubstituted alkene bond, to afford its corresponding 1,4- and 1,3-diol products.

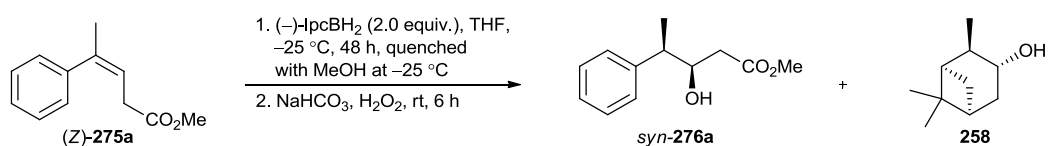
In an attempt to improve the enantioselectivity of the hydroboration reaction of the parent trisubstituted alkene ester **275a**, its asymmetric hydroboration reaction was performed at a significantly lower reaction temperature. Therefore, the reaction was thus repeated as

previously described, with a THF solution containing two equivalents of borane cooled to $-78\text{ }^{\circ}\text{C}$ before addition of ester **275a**. The reaction mixture was then allowed to warm gradually to $15\text{ }^{\circ}\text{C}$ over a period of 42 hours, and oxidised ($\text{H}_2\text{O}_2/\text{NaHCO}_3$) to afford the chiral diol **277a** in a slightly improved 87% ee (Scheme 160, eq 1). Next, the hydroboration reaction of **275a** was carried out at $-25\text{ }^{\circ}\text{C}$ for 48 hours and the excess borane quenched with methanol at $-25\text{ }^{\circ}\text{C}$ before carrying out an oxidative work-up. These conditions were found to result in a highly selective (and complete – no starting material remained) hydroboration, *without* concomitant reduction of the ester functionality having occurred, affording β -hydroxy ester **276a** and isopinocampheol **258** as major products (Scheme 160, eq 2). Following reduction of ester **276a** to the known diol **277a** with LiAlH_4 , the ee was determined as previously described and found to be slightly reduced at 75% ee.



Scheme 160. Low-temperature asymmetric hydroborations of β,γ -unsaturated ester **275a**.

The asymmetric hydroboration of β,γ -unsaturated esters is thus a viable synthetic route to chiral diol products, whilst appropriate control of reaction temperature allows the formation of the corresponding aldol product, **276**. The opposite enantiomer of a given product may be readily accessed upon utilisation of commercially available $(-)\text{-}\alpha$ -pinene to prepare the chiral borane reagent $(+)\text{-IpcBH}_2$, whilst the alternative *syn*-aldol products would be available from reaction of trisubstituted $(Z)\text{-}\beta,\gamma$ -unsaturated esters (Scheme 161).



Scheme 161. Asymmetric hydroboration of $(Z)\text{-}\beta,\gamma$ -unsaturated esters would lead to the formation of *syn*-aldol products.

Although the Knoevenagel reaction of malonic acid to afford β,γ -unsaturated carboxylic acids is known to be applicable to aliphatic aldehydes, in the absence of either the steric bias imparted from a trisubstituted alkene bond or the electronic influence of an aromatic ring, hydroboration of these types of β,γ -unsaturated carboxylic acid derivatives is unlikely to proceed with 100% regioselectivity. Future work involving the screening of more sterically demanding hydroborating agents, such as **294** and **295**, which are derived from the 2-isobutyl and 2-isopropyl homologues of (+)- α -pinene, may afford better enantioselectivities for the hydroboration reactions of esters **275** (Figure 12).³³²

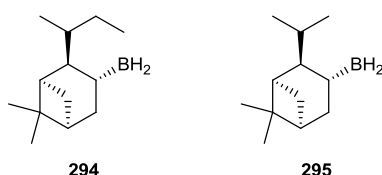
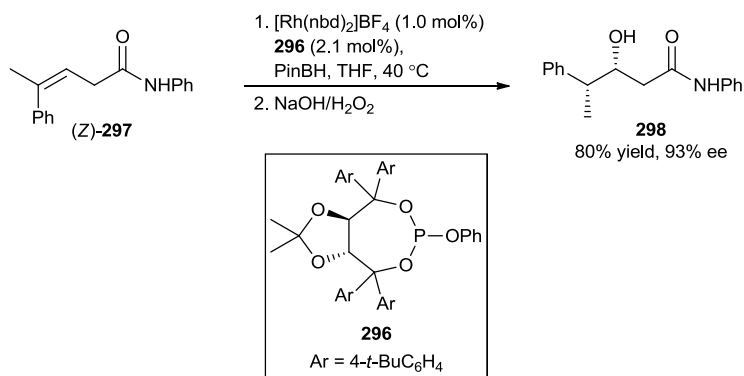


Figure 12. More sterically demanding hydroborating agents derived from (+)- α -pinene homologues.

4.7 Catalytic hydroboration of β,γ -unsaturated amides

During the course of carrying out my studies into asymmetric hydroboration reactions of β,γ -unsaturated esters, Takacs³³³ reported on rhodium-catalysed asymmetric hydroboration of β,γ -unsaturated amides with pinacolborane to afford chiral boronic acid ester intermediates. Oxidation of the resultant boronic esters, with alkaline hydrogen peroxide, afforded their corresponding β -hydroxy amides in good yields and excellent levels of enantioselectivity. The closest example to my β,γ -unsaturated ester substrates (**275a-g**) was the trisubstituted β,γ -unsaturated amide (*Z*)-**297**, which afforded its corresponding β -hydroxy amide **298** in 93% ee (Scheme 162).³³⁴ Although this work broadly resembles the asymmetric hydroboration reactions which I have investigated, my reaction is quite different as it can give tandem reduction to afford chiral diol products, or chiral β -hydroxy esters, depending upon the reaction temperature.



Scheme 162. Rhodium-catalysed asymmetric hydroboration of β,γ -unsaturated amides.

4.8 Summary

My investigation into tandem asymmetric hydroboration-isomerisation reactions quickly revealed that the reversible nature of hydroboration is not compatible with preservation of stereochemical integrity. However, the subsequent attempt to realise this initial objective *via* utilisation of an alternative substrate led directly to the development of a novel application of asymmetric hydroboration reactions for the synthesis of chiral 1,3-diols, or β -hydroxy esters. The limitation of this methodology occurs with disubstituted alkenes, where the decreased steric requirement of the alkene bond results in significantly lower levels of both enantiofacial and regioselectivity.

5. Experimental

5.1 General procedures

Proton magnetic resonance spectra were recorded at 300.22 MHz on a Bruker Avance 300 spectrometer. Chemical shifts (δH) are quoted in parts per million and are referenced to the residual solvent peak. The multiplicities and general assignments of spectroscopic data are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), multiplet (m), broad (br), phenyl (Ph), aromatic (Ar) and apparent (app). Coupling constants are quoted to the nearest 0.1 Hz.

Carbon magnetic resonance spectra were recorded at 75.5 MHz on a Bruker Avance 300 spectrometer. Chemical shifts (δC) are quoted in parts per million and are referenced to the residual solvent peak.

Infrared spectra (4000 cm^{-1} to 0 cm^{-1}) were recorded on a Perkin Elmer 1605 FT spectrometer as thin films; only selected peaks are quoted in v cm^{-1} .

Mass spectra were recorded on a microTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany), using methanol as solvent.

Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter with a path length of 1 dm; concentrations (c) are quoted in g/100 ml.

Analytical thin layer chromatography was carried out using commercially available aluminium backed plates coated with Merck Kieselgel 60 GF₂₅₄. Plates were visualised under UV light (254 nm) or by staining with potassium permanganate or phosphomolybdic acid followed by heating. Flash chromatography was performed under medium pressure using Merck 60 H silica gel (35–70 μm). Samples were loaded either neat or as saturated solutions in an appropriate solvent.

Anhydrous tetrahydrofuran, diethyl ether, toluene and dichloromethane were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at 40–60 °C. Ether refers to diethyl ether. Solvents were evaporated on a Büchi Rotorvapor. All commercially available compounds were used as obtained from the chemical suppliers unless otherwise stated. Reactions requiring anhydrous conditions were performed under nitrogen in oven-dried apparatus. All temperatures quoted are external.

General procedure A: Synthesis of α -methylene aldehydes

According to a literature procedure²⁸² a mixture of the aldehyde (1.0 equiv.), dimethylamine hydrochloride (1.2 equiv.) and 37% aqueous formaldehyde (1.2 equiv.) was stirred at 70 °C for 24 h. After cooling to room temperature, an excess of saturated aqueous NaHCO₃ was added, the aqueous phase separated and extracted with three portions of hexane. The combined organic phases were washed with water, dried (MgSO₄) and the solvent evaporated under reduced pressure to afford the α -methylene aldehyde.

General procedure B: Synthesis of exo-methylene allylic alcohols

The appropriate alkyl halide (0.2 equiv.) was added in one portion to a stirred suspension of magnesium turnings (2.0 equiv.) in dry ether (2 ml.mmol⁻¹) under nitrogen. The mixture was then heated to a gentle reflux and the remaining alkyl halide (1.8 equiv.), diluted with an equal volume of dry ether, was added at a rate sufficient to maintain the reflux. After formation of the Grignard reagent was complete, the solution was cooled to 0 °C in an ice/salt-water bath (water and saturated salt solution in an approximate ratio of 55:45). The appropriate α -methylene aldehyde was then added dropwise. When tlc analysis indicated complete consumption of the aldehyde, the reaction was quenched by the cautious addition of a 50:50 mixture of water and saturated aqueous NH₄Cl solution. The solids were removed by filtration through celite, eluting with fresh ether, and the filtrate transferred to a separatory funnel. The aqueous layer was separated and the organic phase washed successively with 1.0 M aqueous HCl, brine and water, then dried (MgSO₄). The solvent was removed under reduced pressure and the residue purified by column chromatography (SiO₂) to afford the pure allylic alcohol.

General procedure C: Preparation and use of pyridyl-Grignard reagents

Using a modified literature procedure,²⁹⁰ the following were sequentially added to a dry round bottomed flask: 10 ml of an *i*-PrMgCl solution (2.0 M in THF, 20 mmol, 2.0 equiv.), an additional 10 ml of dry THF and the appropriate bromopyridine (20 mmol, 2.0 equiv.). The resulting mixture was stirred at room temperature for 2 hours and then cooled to 0 °C. 2-Methylenebutanal (**206**, 10 mmol, 1.0 equiv.) was then added dropwise and stirring continued at this temperature for a further 4 hours. The reaction was quenched by the

addition of water (20 ml) and extracted with CH_2Cl_2 (3×20 ml). The combined organic phases were washed with water, dried (K_2CO_3) and the solvent removed under reduced pressure. The crude alcohol was then purified by column chromatography (SiO_2).

General procedure D: Oxidation of alcohols to aldehydes/ketones

According to the original literature procedure,³³⁵ the alcohol (10 mmol in 10 ml of dry CH_2Cl_2) was added in one portion to a stirred suspension of pyridinium chlorochromate (1.5 equiv., 15 mmol, 3.23 g) in dry CH_2Cl_2 (20 ml) at room temperature. When tlc analysis indicated complete consumption of the alcohol (1 – 3 h), the reaction mixture was diluted with five volumes of ether and filtered through florisil, eluting with fresh ether. The solvent was then removed under reduced pressure to afford the aldehyde/ketone, which was used without further purification.

General procedure E: Wittig methylenation of ketones

A slightly modified version of a literature procedure³³⁰ was employed: A suspension of methyltriphenylphosphonium bromide (3.20 g, 9.0 mmol, 1.7 equiv.) in dry THF (30 ml) was cooled to 0 °C, followed by the dropwise addition of 3.6 ml BuLi solution (2.5 M in hexanes, 9.0 mmol, 1.7 equiv.). The flask was removed from the cooling bath and stirred at room temperature for two hours, then cooled to 0 °C. A 1.0 M solution of the appropriate ketone (5.3 mmol, 1.0 equiv.) in THF was then added dropwise, the reaction mixture stirred for a further 30 minutes at 0 °C, then removed from the cooling bath and stirred overnight (~16 hours). The reaction mixture was diluted with hexane (50 ml) and filtered through a plug of silica, eluting with a 50:50 mixture of hexane and ether (100 ml). The solvent was then evaporated to afford the pure 1,1'-disubstituted alkene, unless otherwise stated.

General procedure F: Palladium-catalysed isomerisation of exomethylenic allylic alcohols, *O*-allyl ethers, hydrocarbons, α,β -unsaturated aldehydes and ketones

The palladium catalyst, additive (if used) and 80% of the total solvent were placed into a dry Schlenk tube, which was fitted with a rubber septum, and stirred at the appropriate temperature. A balloon attached to a needle-equipped syringe barrel was filled with hydrogen gas and set aside. Vacuum was applied to the Schlenk tube and the tap opened until vigorous bubbling of the solvent was observed, then immediately closed. The hydrogen gas was then transferred to the evacuated tube through the rubber septum. This sequence was repeated twice more and then the appropriate substrate, dissolved in the remaining solvent, was added *via* syringe. The reaction mixture was then stirred for the required time before being filtered through celite and the solvent evaporated under reduced pressure to afford a crude residue which was subsequently analysed directly by ^1H NMR spectroscopy.

General procedure G: Hydroboration-oxidation of substituted arylalkenes using (–)-isopinocampheylborane

According to a modified literature procedure,³⁰⁶ 2IpcBH₂.TMEDA (0.53 equiv., 2.0 mmol, 0.83 g) was dissolved in dry THF (2.5 ml) and BF₃.OEt₂ (1.0 equiv., 3.8 mmol, 0.54 g, 0.47 ml) was added dropwise. After stirring at room temperature for three hours, the mixture was cooled to –20 °C, a 0.3 M THF solution of the arylalkene (0.71 equiv., 2.7 mmol) was added dropwise and stirring was continued at this temperature for 48 hours. The reaction mixture was then brought to room temperature, 3.0 M aqueous NaOH solution (1.2 ml) was added, followed by 30% aqueous H₂O₂ (1.0 ml) and the mixture heated to 55 °C for 1.5 hours. After cooling to room temperature, saturated Na₂CO₃ solution was added and the mixture extracted with ether (3 × 20 ml). The combined organics were washed with water, dried (MgSO₄) and the solvent removed to afford a crude mixture of isopinocampheol **258** and the desired alcohol, which was purified via column chromatography.

General procedure H: Hydroboration-isomerisation-oxidation of substituted arylalkenes using (–)-isopinocampheylborane

The reaction was initially carried out in an identical manner to General Procedure G; however, following completion of the hydroboration stage, the THF was removed under ambient temperature and pressure by a strong flow of nitrogen gas. An equivalent volume of anhydrous diglyme was then added and the mixture stirred thoroughly for one hour. A portion of the crude product mixture was then removed by syringe and oxidised with alkaline hydrogen peroxide, taking care to remove the high-boiling diglyme solvent by washing the ethereal extracts thoroughly with water, then worked-up and purified as previously described. The remainder was then heated at 140 °C for the required time, cooled to room temperature, and worked-up as previously described.

General procedure I: Synthesis of 2-arylpropionaldehydes

A slightly modified version of a literature procedure³³⁰ was employed: A suspension of methoxymethyltriphenylphosphonium chloride (1.7 equiv., 56.6 mmol, 3.07 g) in dry THF (190 ml) was cooled to 0 °C, followed by the dropwise addition of 22.6 ml *n*-BuLi solution (2.5 M in hexanes, 1.7 equiv., 56.6 mmol). The flask was removed from the cooling bath and stirred at room temperature for two hours, then cooled to 0 °C. A 1.0 M solution of the appropriate substituted acetophenone **272** (1.0 equiv., 33.3 mmol) in THF was then added dropwise, the reaction mixture stirred for a further 30 minutes at 0 °C, then removed from the cooling bath and stirred overnight (~16 hours). The reaction mixture was diluted with hexane (320 ml) and filtered through a plug of silica, eluting with a 50:50 mixture of hexane and ether (640 ml). The solvent was then evaporated under reduced pressure to afford the corresponding crude enol ether as an approximately 50:50 mixture of (*E*):(*Z*) isomers (as shown by ¹H NMR spectroscopy), which was subsequently hydrolysed according to a literature procedure.³³¹ A thoroughly stirred mixture of THF (68 ml) and concentrated aqueous HCl (5.5 ml) was added to the crude residue and the resulting mixture refluxed for three hours. After cooling to room temperature, sufficient saturated NaHCO₃ solution was added to neutralise the acid, the organic layer was removed and the aqueous layer was extracted with ether (3 × 50 ml). The combined organic extracts were washed with water, dried (MgSO₄) and the solvent evaporated. The residue was subjected to column chromatography (SiO₂) to afford the pure 2-arylpropionaldehyde **273**.

General procedure J: Synthesis of 4-arylpent-3-enoic acids

According to a literature procedure,³²⁵ dry triethylamine (1.5 equiv., 27.5 mmol, 3.9 ml) and malonic acid (1.0 equiv., 18.3 mmol, 1.90 g) were added to the appropriate 2-arylaldehyde **253** (1.0 equiv., 18.3 mmol), the resulting mixture was refluxed for 16 hours, cooled to room temperature, and then acidified to pH 1 by the addition of dilute aqueous HCl. The solution was extracted with ether (3 × 30 ml) and the combined organic phases were washed with water containing a little NaCl, dried (MgSO₄) and the solvent evaporated under reduced pressure. The residue was dissolved in 0.1 M aqueous NaOH solution, washed with ether (2 × 30 ml), then transferred to a separatory funnel and acidified to pH 1 with dilute aqueous HCl. The precipitated acid was extracted with CH₂Cl₂ (4 × 30 ml), the combined extracts washed once with water containing a little NaCl, dried (MgSO₄) and the solvent evaporated under reduced pressure to afford the crude 4-arylpent-3-enoic acid **274**, which was used in the next step without further purification.

General procedure K: Synthesis of 4-arylpent-3-enoic acid methyl esters

The crude acid (**274**) was dissolved in methanol (0.5 M), 98% H₂SO₄ (0.5 equiv.) was added dropwise with rapid stirring and the resulting solution stirred at room temperature for 24 hours. The acid was neutralised by the addition of excess solid NaHCO₃ and the majority of the methanol evaporated under reduced pressure (the release of dissolved CO₂ can cause extreme bumping at this stage). The residue was partitioned between water and CH₂Cl₂, the aqueous layer extracted with CH₂Cl₂, then the combined organics were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified *via* column chromatography (SiO₂) to afford the respective (*E*)- and (*Z*)-isomers of the methyl 4-arylpent-3-enoate **275**.

General procedure L: Asymmetric hydroboration of β,γ -unsaturated esters using (–)-isopinocampheylborane

BF₃·OEt₂ (2.0 equiv., 5.26 mmol, 0.65 ml) was added dropwise to a solution of 2IpcBH₂·TMEDA **257** (1.05 equiv., 2.76 mmol, 1.15 g) in 3.8 ml of dry THF. The resulting mixture was stirred at room temperature for three hours and then cooled to

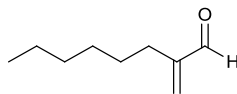
approximately $-17\text{ }^{\circ}\text{C}$ in a mixture of methanol and crushed ice. The surface of the slurry was covered with tin foil, wrapped with cotton wool and then wrapped again with tin foil. A solution of the ester **275** (1.0 equiv., 2.63 mmol) in THF (1.0 ml) was then added dropwise and the reaction mixture allowed to warm slowly to $0\text{ }^{\circ}\text{C}$, over approximately 16 hours. The intermediate organoboranes were then oxidised via treatment with 30% aqueous H_2O_2 (13.8 ml) and saturated NaHCO_3 solution (84 ml) followed by stirring at room temperature for six hours. Then the mixture was extracted with ether, the combined organics washed with water, dried (MgSO_4) and the solvent evaporated under reduced pressure to afford a mixture of isopinocampheol **258** and the corresponding diol **277**, which was isolated *via* column chromatography (SiO_2).

General procedure M: Determination of the enantiomeric excesses of diols 277a-h and 293 via a chiral derivatisation protocol

According to a literature procedure,³²⁷ two samples of the diol (1 – 40 mg, 1.0 equiv.) were placed in small sample vials. CDCl_3 (0.8 ml) and 2-formylphenyl boronic acid **280** (1.1 equiv.) were added to each vial, followed by either racemic α -methylbenzylamine or enantiomerically pure (*S*)-(-)- α -methylbenzylamine **281** (1.2 equiv.). A small quantity of MgSO_4 was then added and the contents of each vial were mixed thoroughly. After being allowed to stand for 10 minutes, the resulting mixtures were filtered through cotton wool into NMR tubes and analysed by 500 MHz ^1H NMR spectroscopy. The enantiomeric excess of the diol **277** was then determined *via* integration of the respective imine proton resonances of its corresponding diastereomeric derivatives.

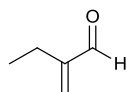
5.2 Synthesis of 2-methylene aldehydes

2-Methyleneoctanal **197**³³⁶



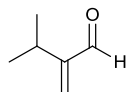
General procedure A was followed, using *n*-octanal (10.0 ml, 8.20 g), to afford the title compound as a pale yellow oil (7.53 g, 84%); ¹H NMR (300 MHz, CDCl₃) δ 9.47 (1H, s, CHO), 6.19-6.16 (1H, m, C=CH_AH_B), 5.92-5.90 (1H, m, C=CH_AH_B), 2.21-2.12 (2H, m, C₅H₁₁CH₂), 1.44-1.14 (8H, m, (CH₂)₄), 0.86-0.76 (3H, m, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 195.2, 150.9, 134.2, 32.0, 29.3, 28.1, 28.1, 22.9, 14.4; IR (neat): 1698 (C=O) (cm⁻¹).

2-Methylenebutanal **206**³³⁷



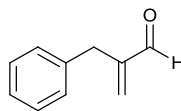
General procedure A was followed, using *n*-butyraldehyde (20.0 ml, 16.0 g). The product was isolated *via* extraction of the quenched reaction mixture with ether, followed by fractional distillation to afford the title compound as a colourless oil (bp 91 °C, 8.40 g, 45%); ¹H NMR (300 MHz, CDCl₃) δ 9.55 (1H, s, CHO), 6.22-6.27 (1H, m, C=CH_AH_B), 5.96-6.00 (1H, m, C=CH_AH_B), 2.26 (2H, q, *J* = 7.4 Hz, CH₃CH₂), 1.07 (3H, t, *J* = 7.4 Hz, CH₃CH₂).

3-Methyl-2-methylenebutanal **207**³³⁸



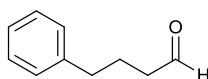
General procedure A was followed, using isovaleraldehyde (20.0 ml, 16.06 g). The product was isolated *via* extraction of the quenched reaction mixture with ether, followed by fractional distillation to afford the title compound as a colourless oil (bp 109 °C, 10.25 g, 56%); ¹H NMR (300 MHz, CDCl₃) δ 9.46 (1H, s, CHO), 6.17 (1H, d, *J* = 0.9 Hz, C=CH_AH_B), 5.88 (1H, s, C=CH_AH_B), 2.73 (septet of d, 1H, *J* = 6.8 and 0.9 Hz, (CH₃)₂CH), 1.01 (6H, d, *J* = 6.8 Hz, (CH₃)₂CH); ¹³C NMR (75 MHz, CDCl₃) δ 195.1, 156.9, 132.6, 46.0, 21.7; IR (neat): 1698 (C=O) (cm⁻¹).

2-Benzylacrylaldehyde **208**³³⁸



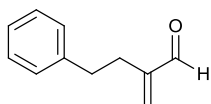
General procedure A was followed, using hydrocinnamaldehyde (10.0 ml, 10.19 g), to form the title compound as a pale yellow oil, (8.77 g, 79%); ¹H NMR (300 MHz, CDCl₃) δ 9.53 (1H, s, CHO), 7.26-7.06 (5H, m, Ph), 6.04-6.01 (1H, m, C=CH_AH_B), 6.00-5.97 (1H, m, C=CH_AH_B), 3.49 (2H, s, PhCH₂); ¹³C NMR (75 MHz, CDCl₃) δ 194.4, 150.2, 138.5, 129.6, 129.0, 126.9, 125.7, 21.9; IR (neat): 1690 (C=O) (cm⁻¹).

4-Phenylbutanal **211**³³⁹



General Procedure D was followed, using 4-phenyl-1-butanol (10.0 g) and PCC (21.52 g) to afford the title compound as a colourless oil (9.08 g, 92%) which was used without further purification; ¹H NMR (300 MHz, CDCl₃) δ 9.77 (1H, t, *J* = 1.6 Hz, CHO), 7.36-7.13 (5H, m, Ph), 2.68 (2H, t, *J* = 7.6 Hz, PhCH₂), 2.47 (2H, td, *J* = 7.3 and 1.5 Hz, CH₂CHO), 1.98 (2H, tt, *J* = 7.6 and 7.3 Hz, CH₂CH₂CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 202.7, 141.6, 128.9, 126.5, 43.5, 35.4, 24.1.

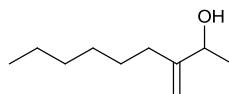
2-Methylene-4-phenylbutanal **212**



General procedure A was followed, using 4-phenylbutanal (**211**, 8.80 g), to form the title compound as a pale yellow oil (7.90 g, 83%); ^1H NMR (300 MHz, CDCl_3) δ 9.47 (1H, s, CHO), 7.24-7.04 (5H, m, Ph), 6.12-6.10 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.92-5.90 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 2.73-2.65 (2H, m, PhCH_2), 2.54-2.45 (2H, m, PhCH_2CH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 195.0, 149.7, 141.5, 135.1, 128.9, 128.8, 126.5, 34.4, 30.1; IR (neat): 1692 ($\text{C}=\text{O}$) (cm^{-1}).

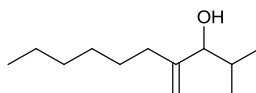
5.3 Synthesis of exomethylenic allylic alcohols

3-Methylenenonan-2-ol **198a**³⁴⁰



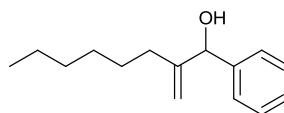
General procedure B was followed, using 2-methyleneoctanal (**197**, 5.00 g) and methyl iodide (10.12 g, 4.4 ml) to afford the title compound as a colourless oil (5.00 g, 79%); ¹H NMR (300 MHz, CDCl₃) δ 4.96 (1H, s, C=CH_AH_B), 4.75-4.72 (1H, m, C=CH_AH_B), 4.18 (1H, q, *J* = 5.9 Hz, CH(OH)), 2.08-1.86 (2H, m, C₅H₁₁CH₂), 1.51 (1H, br. s, OH), 1.46-1.15 (11H, m, CH₃(CH₂)₄ and CH(OH)CH₃), 0.89-0.74 (3H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 154.0, 108.3, 71.4, 32.2, 32.2, 29.6, 28.4, 23.0, 22.6, 14.5; IR (neat): 3350 (O–H) (cm⁻¹).

2-Methyl-4-methylenedecan-3-ol **198b**



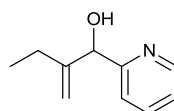
General procedure B was followed, using 2-methyleneoctanal (**197**, 7.80 g) and isopropyl iodide (18.91 g, 11.1 ml) to afford the title compound as a colourless oil (5.23 g, 51%); ¹H NMR (300 MHz, CDCl₃) δ 4.91 (1H, s, C=CH_AH_B), 4.82-4.79 (1H, m, CCH_AH_B), 3.68 (1H, d, *J* = 6.5 Hz, CH(OH)), 2.07-1.80 (2H, m, C₅H₁₁CH₂), 1.80-1.66 (1H, m, CH(CH₃)₂), 1.47-1.16 (8H, m, CH₃(CH₂)₄), 0.86 (3H, d, *J* = 6.7 Hz, CH₃CHCH₃), 0.82 (3H, obs. t, CH₃CH₂), 0.81 (3H, d, *J* = 6.8 Hz, CH₃CHCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 151.7, 110.5, 81.5, 32.2, 31.8, 31.5, 29.7, 28.3, 23.0, 20.1, 17.7, 14.5; IR (neat): 3394 (O–H) (cm⁻¹); HRMS (ES): *m/z* [C₁₂H₂₃O]⁺ requires 183.1749, found 183.1739.

2-Methylene-1-phenyloctan-1-ol **198c**³⁴¹



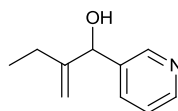
To a dry round bottom flask was added 72 ml of PhMgBr solution (1.0 M in THF, 72 mmol, 2.0 equiv.), followed by an equal volume of dry THF. The resulting solution was cooled to 0 °C and 2-methyleneoctanal (**197**, 5.0 g, 35.6 mmol, 1.0 equiv.) was added dropwise *via* syringe. When tlc analysis indicated complete consumption of the aldehyde, saturated aqueous ammonium chloride solution (10 ml) was added and the mixture stirred at room temperature for 15 m followed by the addition of ether (150 ml). The whole mixture was transferred to a separatory funnel and the organic layer was washed successively with 1.0 M HCl_(aq) (50 ml), brine (50 ml) and water (50 ml). The combined organic fractions were dried (MgSO₄) and the solvent removed under reduced pressure. The crude product was purified by column chromatography to afford the title compound as a colourless oil (5.06 g, 65%); ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.26 (5H, m, Ph), 5.27 (1H, s, C=CH_AH_B), 5.15 (1H, s, C=CH_AH_B), 4.99 (1H, s, CH(OH)), 2.07-1.79 (3H, m, C₅H₁₁CH₂ and OH), 1.48-1.15 (8H, m, CH₃(CH₂)₄), 0.93-0.83 (3H, m, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 151.6, 142.6, 128.8, 128.1, 127.1, 110.0, 77.8, 32.2, 32.1, 29.5, 28.2, 23.0, 14.5; IR (neat): 3360 (O–H) (cm⁻¹); HRMS (ES): m/z [C₁₅H₂₂NaO]⁺ requires 241.1568, found 241.1560.

2-Methylene-1-(pyridin-2-yl)butan-1-ol **198d**



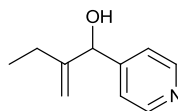
General Procedure C was followed, using 2-methylenebutanal (**206**, 0.84 g) and 2-bromopyridine (3.16 g, 1.9 ml) to afford the title compound as a colourless oil (0.71 g, 44%); ¹H NMR (300 MHz, CDCl₃) δ 8.41-8.47 (1H, m, Ar), 7.57 (1H, td, *J* = 7.7 and 1.7 Hz, Ar), 7.19-7.24 (1H, m, Ar), 7.11 (1H, ddd, *J* = 7.4, 5.1 and 1.0 Hz, Ar), 5.12-5.15 (2H, m, C=CH₂), 4.90-4.93 (1H, m, CH(OH)), 1.89-2.08 (1H, m, CH₃CH_AH_B), 1.54-1.73 (1H, m, CH₃CH_AH_B), 0.89 (3H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 160.4, 152.4, 148.1, 137.1, 122.7, 121.3, 111.8, 77.5, 23.1, 12.3; IR (neat): 3412 (O–H) cm⁻¹; HRMS (ES): m/z [C₁₀H₁₃NNaO]⁺ requires 186.0895, found 186.0886.

2-Methylene-1-(pyridin-3-yl)butan-1-ol 198e



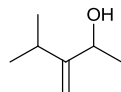
3-Bromopyridine was purified by distillation under reduced pressure (bp 55 °C, 10 mmHg) and then General Procedure C was followed, using 2-methylenebutanal (**206**, 0.84 g) and 3-bromopyridine (3.16 g, 1.9 ml) to afford the title compound as a colourless oil (0.97 g, 60%); ^1H NMR (300 MHz, CDCl_3) δ 8.48 (1H, d, $J = 1.8$ Hz, Ar), 8.40 (1H, dd, $J = 4.8$ and 1.5 Hz, Ar), 7.66 (1H, dtd, $J = 7.9$, 1.9 and 0.5 Hz, Ar), 7.20 (1H, ddd, $J = 7.8$, 4.9 and 0.5 Hz, Ar), 5.21-5.19 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.15 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.96-4.93 (1H, m, $\text{CH}(\text{OH})$), 3.18 (1H, br. s, OH), 2.00-1.71 (2H, m, CH_3CH_2), 0.93 (3H, t, $J = 7.4$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 152.4, 148.8, 148.5, 138.4, 134.9, 123.8, 110.3, 75.6, 24.5, 12.4; IR (neat): 3189 (O–H), 1024 (C–O) cm^{-1} ; HRMS (ES): m/z [$\text{C}_{10}\text{H}_{13}\text{NNaO}$] $^+$ requires 186.0895, found 186.0892.

2-Methylene-1-(pyridin-4-yl)butan-1-ol 198f



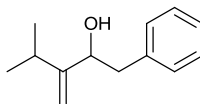
4-Bromopyridine hydrochloride (5.0 g) was dissolved in water, the resulting solution placed into a separatory funnel and the pH adjusted to around 10 with saturated Na_2CO_3 solution. The solution was then extracted thoroughly with ether, dried (K_2CO_3) and the solvent removed under reduced pressure to afford the unstable 4-bromopyridine freebase (3.58 g). General Procedure C was then followed using 2-methylenebutanal (**206**, 0.84 g) and 4-bromopyridine (3.16 g) to afford the title compound as an off-white solid (0.55 g, 34%); ^1H NMR (300 MHz, CDCl_3) δ 8.48-8.53 (2H, m, Ar), 7.30-7.35 (2H, m, Ar), 5.19-5.25 (2H, m, $\text{C}=\text{CH}_2$), 4.99-5.03 (1H, m, $\text{CH}(\text{OH})$), 3.34 (1H, br. s, OH), 1.95-2.12 (1H, m, $\text{CH}_3\text{CH}_\text{A}\text{H}_\text{B}$), 1.74-1.91 (1H, m, $\text{CH}_3\text{CH}_\text{A}\text{H}_\text{B}$), 1.00 (3H, t, $J = 7.3$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 152.2, 152.1, 149.8, 121.9, 111.3, 76.9, 23.9, 12.3; IR (neat): 3075 (O–H), 1063 (C–O) cm^{-1} ; HRMS (ES): m/z [$\text{C}_{10}\text{H}_{14}\text{NO}$] $^+$ requires 164.1075, found 164.1070.

4-Methyl-3-methylenepentan-2-ol **198g**³⁴²



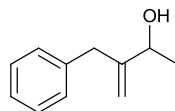
General procedure B was followed, using 3-methyl-2-methylenebutanal (**207**, 5.0 g) and methyl iodide (14.46 g, 6.3 ml) to afford the title compound as a colourless oil (4.77 g, 82%); ¹H NMR (300 MHz, CDCl₃) δ 5.01-4.97 (1H, m, C=CH_AH_B), 4.80 (1H, s, C=CH_AH_B), 4.22 (1H, q, *J* = 6.4 Hz, CH(OH)), 2.33-2.15 (1H, m, CH(CH₃)₂), 1.54 (1H, br. s, OH), 1.23 (3H, d, *J* = 6.4 Hz, CH₃CH(OH)), 1.00 (6H, app. t, *J* = 6.7 Hz, (CH₃)₂CH); ¹H NMR (75 MHz, CDCl₃) δ 160.8, 106.3, 70.5, 30.6, 23.5, 23.2, 23.0; IR (neat): 3352 (O–H) (cm⁻¹); HRMS (ES): *m/z* [C₇H₁₄NaO]⁺ requires 137.0937, found 137.0950.

4-Methyl-3-methylene-1-phenylpentan-2-ol **198h**³⁴³



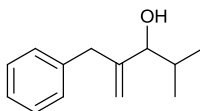
General procedure B was followed, using 3-methyl-2-methylenebutanal (**207**, 5.0 g) and benzyl bromide (17.43 g, 12.1 ml) to afford the title compound as a colourless oil (7.17 g, 74%); ¹H NMR (300 MHz, CDCl₃) δ 7.27-7.12 (5H, m, Ph), 5.05-5.03 (1H, m, C=CH_AH_B), 4.88 (1H, s, C=CH_AH_B), 4.22 (1H, dd, *J* = 8.8 and 3.7 Hz, CH(OH)), 2.87 (1H, dd, *J* = 13.7 and 3.9 Hz, CH_AH_BPh), 2.65 (1H, dd, *J* = 13.7 and 8.8 Hz, CH_AH_BPh), 2.32-2.17 (1H, m, CH(CH₃)₂), 1.55 (1H, br. s, OH), 1.03 (3H, d, *J* = 4.9 Hz, CH₃CHCH₃), 1.01 (3H, d, *J* = 4.9 Hz, CH₃CHCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 158.8, 139.0, 129.8, 128.9, 126.9, 107.8, 75.2, 43.9, 31.2, 23.5, 22.8; IR (neat): 3402 (O–H) (cm⁻¹); HRMS (ES): *m/z* [C₁₃H₁₈NaO]⁺ requires 213.1255, found 213.1249.

3-Benzylbut-3-en-2-ol **198i**³⁴⁴



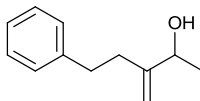
General procedure B was followed, using 2-benzylacrylaldehyde (**208**, 5.0 g) and methyl iodide (9.71 g, 4.3 ml) to afford the title compound as a colourless oil (4.66 g, 84%); ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.19 (5H, m, Ph), 5.17 (1H, s, C=CH_AH_B), 4.78-4.75 (1H, m, C=CH_AH_B), 4.26 (1H, q, *J* = 6.5 Hz, CH(OH)), 3.49 (1H, d, *J* = 15.5 Hz, PhCH_AH_B), 3.37 (1H, d, *J* = 15.5 Hz, PhCH_AH_B), 1.74 (1H, br. s, OH), 1.32 (3H, d, *J* = 6.5 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 153.0, 139.9, 129.6, 128.8, 126.6, 111.3, 70.6, 39.4, 22.6; IR (neat): 3350 (O–H) (cm⁻¹); HRMS (ES): *m/z* [C₁₁H₁₄NaO]⁺ requires 185.0942, found 185.0944.

2-Benzyl-4-methylpent-1-en-3-ol **198j**



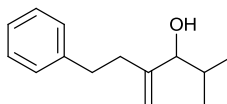
General procedure B was followed, using 2-benzylacrylaldehyde (**208**, 5.0 g) and isopropyl iodide (11.63 g, 6.8 ml) to afford the title compound as a colourless oil (4.82 g, 74%); ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.08 (5H, m, Ph), 5.00 (1H, s, CCH_AH_B), 4.67-4.64 (1H, m, CCH_AH_B), 3.71 (1H, d, *J* = 6.5 Hz, CH(OH)), 3.37 (1H, d, *J* = 15.7 Hz, CH_AH_BPh), 3.18 (1H, d, *J* = 15.7 Hz, CH_AH_BPh), 1.87-1.71 (1H, m, CH(CH₃)₂), 1.48 (1H, br. s, OH), 0.87 (3H, d, *J* = 6.7 Hz, CH₃CHCH₃), 0.82 (3H, d, *J* = 6.8 Hz, CH₃CHCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 151.0, 139.8, 129.7, 128.8, 126.6, 113.4, 80.8, 39.0, 31.6, 20.0, 17.7; IR (neat): 3402 (O–H) (cm⁻¹); HRMS (ES): *m/z* [C₁₃H₁₈NaO]⁺ requires 213.1255, found 213.1252.

3-Methylene-5-phenylpentan-2-ol **198k**



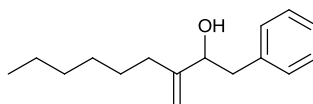
General procedure B was followed, using 2-methylene-4-phenylbutanal (**212**, 3.0 g) and methyl iodide (5.32 g, 2.3 ml) to afford the title compound as a colourless oil (2.64 g, 80%); ^1H NMR (300 MHz, CDCl_3) δ 7.26-7.06 (5H, m, Ph), 5.05-4.98 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.84-4.77 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.19 (1H, q, $J = 6.4$ Hz, $\text{CH}(\text{OH})$), 2.76-2.68 (2H, m, PhCH_2), 2.41-2.18 (2H, m, PhCH_2CH_2), 1.52 (1H, br. s, OH), 6.43 (3H, d, $J = 6.4$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 153.1, 142.4, 128.8, 126.3, 109.2, 71.5, 35.0, 33.7, 22.6; IR (neat): 3351 (O–H) (cm^{-1}); HRMS (ES): m/z [$\text{C}_{12}\text{H}_{16}\text{NaO}$] $^+$ requires 199.1099, found 199.1083.

2-Methyl-4-methylene-6-phenylhexan-3-ol **198l**



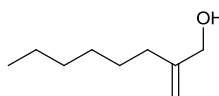
General procedure B was followed, using 2-methylene-4-phenylbutanal (**212**, 4.0 g) and isopropyl iodide (8.49 g, 5.0 ml) to afford the title compound as a colourless oil (3.01 g, 59%); ^1H NMR (300 MHz, CDCl_3) δ 7.23-7.04 (5H, m, Ph), 4.97 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.91-4.87 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.67 (1H, d, $J = 6.9$ Hz, $\text{CH}(\text{OH})$), 2.76-2.69 (2H, m, PhCH_2), 2.40-2.26 (1H, m, $\text{PhCH}_2\text{CH}_\text{A}\text{H}_\text{B}$), 2.25-2.10 (1H, m, $\text{PhCH}_2\text{CH}_\text{A}\text{H}_\text{B}$), 1.81-1.63 (1H, m, $(\text{CH}_3)_2\text{CH}$), 1.50 (1H, br. s, OH), 0.85 (3H, d, $J = 6.6$ Hz, CH_3CHCH_3), 0.79 (3H, d, $J = 6.8$ Hz, CH_3CHCH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 150.9, 142.5, 128.8, 126.3, 111.4, 81.7, 34.8, 33.4, 31.7, 20.1, 17.9; IR (neat): 3410 (O–H) (cm^{-1}); HRMS (ES): m/z [$\text{C}_{14}\text{H}_{20}\text{NaO}$] $^+$ requires 227.1412, found 227.1400.

3-Methylene-1-phenylnonan-2-ol **198m**



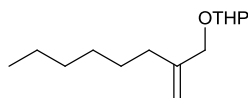
General procedure B was followed, using 2-methyleneoctanal (**197**, 5.0 g) and benzyl bromide (12.2 g, 8.5 ml), to form the title compound as a colourless oil (5.88 g, 71%); ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.20 (5H, m, Ph), 5.07 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.92-4.88 (1H, m, $\text{CCH}_\text{A}\text{H}_\text{B}$), 4.30 (1H, dd, $J = 8.8$ and 4.1 Hz, $\text{CH}(\text{OH})$), 2.96 (1H, dd, $J = 13.7$ and 4.2 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 2.76 (1H, dd, $J = 13.7$ and 8.8 Hz, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$), 2.24-2.01 (2H, m, $\text{C}_5\text{H}_{11}\text{CH}_2$), 1.67 (1H, br. s, OH), 1.60-1.26 (8H, m, $\text{CH}_3(\text{CH}_2)_4$), 0.97-0.84 (3H, m, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 151.9, 138.9, 129.8, 128.9, 126.9, 109.9, 76.3, 43.2, 32.5, 32.2, 29.7, 28.4, 23.1, 14.5; IR (neat): 3401 (O–H) (cm^{-1}); HRMS (ES): m/z [$\text{C}_{16}\text{H}_{24}\text{NaO}$] $^+$ requires 255.1725, found 255.1714.

2-Methyleneoctan-1-ol **198n**³⁴⁵



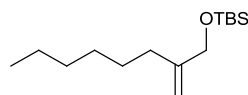
A solution of 2-methyleneoctanal (**197**, 10.0 g, 71.3 mmol) in dry ether (60 ml) was added dropwise to a stirred suspension of LiAlH_4 (1.46 g, 38.5 mmol) in dry ether (120 ml) at 0°C . The mixture was stirred for 2 h at 5°C , then 1.5 ml water, 1.5 ml 15% aqueous NaOH and 4.5 ml water were slowly added in succession. The inorganic salts were filtered off, the aqueous phase was extracted with ether and the combined organic fractions were washed with brine and water, dried (MgSO_4) and the solvent removed under reduced pressure. The residue was purified by column chromatography (SiO_2) to afford the title compound as a colourless oil (7.81 g, 77%); ^1H NMR (300 MHz, CDCl_3) δ 4.95-4.92 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.81-4.77 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.00 (2H, d, $J = 5.8$ Hz, CH_2OH), 2.02-1.94 (2H, m, $\text{C}_5\text{H}_{11}\text{CH}_2$), 1.54 (1H, t, $J = 5.8$ Hz, OH), 1.44-1.14 (8H, m, $\text{CH}_3(\text{CH}_2)_4$), 0.87-0.74 (3H, m, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 149.7, 109.3, 66.3, 33.4, 32.1, 29.5, 28.1, 23.0, 14.5; IR (neat): 3326 (O–H) (cm^{-1}).

2-(2-Methyleneoctyloxy)tetrahydro-2H-pyran **198o**



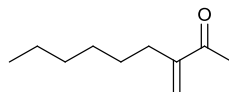
To a solution of 2-methyleneoctan-1-ol (**198n**, 1.0 g, 7.0 mmol) in CH_2Cl_2 (72 ml), dihydropyran (0.71 ml, 7.74 mmol) was added, followed by pyridinium *para*-toluenesulphonate (0.177 g, 0.70 mmol) and the reaction mixture was stirred at room temperature overnight. After addition of a saturated NaHCO_3 solution the reaction mixture was diluted with CH_2Cl_2 , the organic layer washed with water, dried (MgSO_4), the solvent removed under reduced pressure and the residue purified by column chromatography (SiO_2) to afford the title compound as a colourless oil (1.27 g, 80%); ^1H NMR (300 MHz, CDCl_3) δ 4.96 (1H, s, $\text{CCH}_\text{A}\text{H}_\text{B}$), 4.82 (1H, s, $\text{CCH}_\text{A}\text{H}_\text{B}$), 4.59-4.52 (1H, m,), 4.14-4.06 (1H, m,), 3.88-3.75 (2H, m,), 3.50-3.40 (1H, m,), 2.04-1.93 (2H, m,), 1.87-1.31 (8H, m,), 1.31-1.17 (6H, m,), 0.86-0.75 (3H, m,); ^{13}C NMR (75 MHz, CDCl_3) δ 146.7, 111.1, 98.1, 70.1, 62.5, 33.7, 32.1, 31.0, 29.5, 28.0, 25.9, 23.0, 19.8, 14.5; IR (neat): 1036 (O–C–O) (cm^{-1}); HMRS (ES): m/z [$\text{C}_{14}\text{H}_{26}\text{NaO}_2$] $^+$ requires 249.1831, found 249.1813.

tert-Butyldimethyl(2-methyleneoctyloxy)silane **198p**



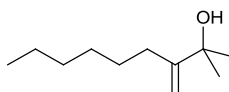
To a solution of 2-methyleneoctan-1-ol (**198n**, 1.0 g, 7.0 mmol) in CH_2Cl_2 (72 ml) were added imidazole (1.46 g, 21.4 mmol) and DMAP (0.13 g, 1.1 mmol), followed by (*tert*-butyldimethyl)silyl chloride (2.15 g, 14.3 mmol) in CH_2Cl_2 (5 ml). After stirring for 24 hours, the reaction mixture was partitioned between saturated aqueous NaHCO_3 and CH_2Cl_2 . The organic layer was separated, washed with water and dried (MgSO_4). The solvent was removed under reduced pressure and the residue purified by column chromatography to afford the title compound as a colourless oil (1.53 g, 85%); ^1H NMR (300 MHz, CDCl_3) δ 4.97-4.91 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.75-4.71 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 3.99 (2H, s, CH_2O), 1.97-1.88 (2H, m, $\text{C}_5\text{H}_{11}\text{CH}_2$), 1.43-1.14 (8H, m, $\text{CH}_3(\text{CH}_2)_4$), 0.89-0.77 (12H, m, CH_3CH_2 and $(\text{CH}_3)_3\text{C}$), 0.00 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 149.3, 108.6, 66.3, 33.2, 32.1, 29.5, 28.2, 26.3, 23.0, 18.8, 14.5, -4.5; IR (neat): 1252 ($\text{Si}-\text{CH}_3$), 1086 ($\text{Si}-\text{O}$) (cm^{-1}).

3-Methylenenonan-2-one **201a**³⁴⁶



General Procedure D was followed, using 3-methylenenonan-2-ol (**198a**, 4.0 g) and PCC (5.52 g), to afford the title compound as a pale yellow oil (2.92 g, 74%) which was used without further purification; ^1H NMR (300 MHz, CDCl_3) δ 5.98 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.76-5.71 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 2.32 (3H, s, CH_3CO), 2.28-2.20 (2H, m, $\text{C}_5\text{H}_{11}\text{CH}_2$), 1.45-1.20 (8H, m, $\text{CH}_3(\text{CH}_2)_4$), 0.94-0.80 (3H, m, CH_3CH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 200.3, 149.8, 124.9, 32.0, 30.9, 29.4, 28.8, 26.3, 23.0, 14.4; IR (neat): 1681 ($\text{C}=\text{O}$) (cm^{-1}).

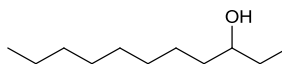
2-Methyl-3-methylenenonan-2-ol **198q**³⁴⁷



General procedure B was followed, using 3-methylenenonan-2-one (**201a**, 2.0 g) and methyl iodide (3.68 g, 1.6 ml) to afford the title compound as a colourless oil (1.83 g, 83%); ^1H NMR (300 MHz, CDCl_3) δ 5.12-5.09 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 4.79-4.76 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 2.11-2.02 (2H, m, $\text{C}_5\text{H}_{11}\text{CH}_2$), 1.57-1.22 (15H, m, $\text{CH}_3(\text{CH}_2)_4$, $\text{C}(\text{CH}_3)_2$ and OH), 0.94-0.83 (3H, m, CH_3CH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 156.7, 106.9, 73.9, 32.2, 31.5, 29.8, 29.6, 29.2, 23.0, 14.5; IR (neat): 3411 ($\text{O}-\text{H}$) (cm^{-1}).

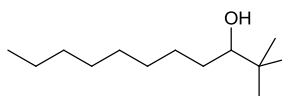
5.4 Synthesis of exomethylenic hydrocarbons

Undecan-3-ol **220b**³⁴⁸



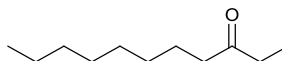
A 0.5 M solution of EtMgBr in ether (116.4 ml, 58.2 mmol) was prepared *via* dilution of the commercially available reagent and cooled to 0 °C, followed by the dropwise addition of nonanal (4.14 g, 5.0 ml, 29.1 mmol, 0.5 equiv.). After stirring for one hour, the reaction was quenched by the cautious addition of 50% saturated NH₄Cl solution and transferred to a separatory funnel. Sufficient 1.0 M HCl and water were added to dissolve the precipitated salts, the organic layer was separated and the aqueous fraction extracted with ether (3 × 50 ml). The combined organics were washed successively with saturated NaHCO₃ solution (50 ml) and water (50 ml), dried (MgSO₄) and the solvent evaporated to afford the title compound as a colourless oil (4.61 g, 92%); ¹H NMR (300 MHz, CDCl₃) δ 3.46-3.58 (1H, m, CH(OH)), 1.19-1.56 (16H, m, (CH₂)₇ and CH(OH)CH₂CH₃), 0.93 (3H, t, *J* = 7.4 Hz, CH(OH)CH₂CH₃), 0.84-0.90 (3H, m, CH₃CH₂CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 73.4, 37.0, 31.9, 30.2, 29.7, 29.6, 29.3, 25.7, 22.7, 14.1, 9.9; IR (neat): 3345 (O–H), 1114 (C–O) (cm⁻¹).

2,2-Dimethylundecan-3-ol **220c**³⁴⁹



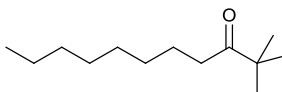
To 82.2 ml of dry ether was added 34.2 ml of a commercially available *t*-BuLi solution (1.7 M in pentane, 58.1 mmol) to afford a final concentration of ~0.5 M. The resulting solution was cooled to 0 °C, followed by the dropwise addition of nonanal (4.14 g, 5.0 ml, 29.1 mmol, 0.5 equiv.). The reaction mixture was stirred for one hour and worked up as described above for **220b** to afford the title compound as a colourless oil (5.13 g, 88%); ¹H NMR (300 MHz, CDCl₃) δ 3.19 (1H, app. d, *J* = 10.0 Hz, CH(OH)), 1.18-1.66 (14H, m, (CH₂)₇), 0.80-0.97 (12H, m, CH₃CH₂ and C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ 80.0, 34.9, 31.9, 31.5, 29.8, 29.7, 29.4, 27.1, 25.7, 22.7, 14.2.

Undecan-3-one **221b**³⁵⁰



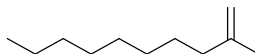
According to General Procedure D, undecan-3-ol (**220b**, 4.0 g) was oxidised with PCC (7.51 g) to afford the title compound as a colourless oil (2.65 g, 67%) which was used without further purification; ¹H NMR (300 MHz, CDCl₃) δ 2.30-2.43 (4H, m, CH₂C(O)CH₂), 1.45-1.59 (2H, m, CH₂CH₂C(O)), 1.14-1.32 (10H, m, (CH₂)₅), 1.00 (3H, t, *J* = 7.3 Hz, CH₃CH₂C(O)), 0.78-0.87 (3H, m, CH₃(CH₂)₇); ¹³C NMR (75 MHz, CDCl₃) δ 211.7, 42.4, 35.8, 31.8, 29.3, 29.2, 29.1, 23.9, 22.6, 14.0, 7.8.

2,2-Dimethylundecan-3-one **221c**³⁵³



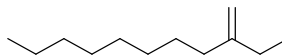
According to General Procedure D, 2,2-dimethylundecan-3-ol (**220c**, 5.0 g) was oxidised with PCC (8.08 g) to afford the title compound as a colourless oil (3.07 g, 62%) which was used without further purification; ¹H NMR (300 MHz, CDCl₃) δ 2.47 (2H, t, *J* = 7.3 Hz, CH₂CO), 1.47-1.62 (2H, m, CH₂CH₂CO), 1.19-1.37 (10H, m, alkyl), 1.12 (9H, s, (CH₃)₃C), 0.94-0.83 (3H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 216.3, 44.1, 36.5, 31.9, 29.5, 29.4, 29.2, 26.4, 24.0, 22.7, 14.1.

2-Methyldec-1-ene **222a**³³⁰



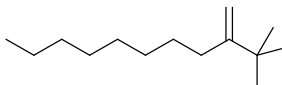
According to General Procedure E, 2-decanone (1.65 g, 2.0 ml) was methylenated to afford the title compound as a colourless oil (0.93 g, 57%) which was used without further purification; ¹H NMR (300 MHz, CDCl₃) δ 4.68 (1H, s, C=CH_AH_B), 4.66 (1H, s, C=CH_AH_B), 2.00 (2H, t, *J* = 7.5 Hz, CH₂C), 1.71 (3H, s, CH₃C), 1.22-1.48 (12H, m, (CH₂)₆), 0.84-0.92 (3H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 146.4, 109.5, 37.9, 31.9, 29.6, 29.4, 29.3, 27.7, 22.7, 22.4, 14.2; IR (neat): 2981 (C=CH₂), 1650 (C=C) (cm⁻¹).

3-Methyleneundecane **222b**³⁵¹



According to General Procedure E, 3-undecanone (**221b**, 2.50 g) was methylenated to afford the title compound as a colourless oil (1.31 g, 53%) which was used without further purification; ¹H NMR (300 MHz, CDCl₃) δ 4.68-4.72 (2H, m, C=CH₂), 1.97-2.08 (4H, m, CH₂C(=CH₂)CH₂), 1.19-1.50 (12H, m, (CH₂)₆), 1.03 (3H, t, *J* = 7.5 Hz, CH₃CH₂C), 0.85-0.94 (3H, m, CH₃(CH₂)₇); ¹³C NMR (75 MHz, CDCl₃) δ 151.9, 107.2, 36.3, 31.9, 29.6, 29.5, 29.3, 28.7, 27.9, 22.7, 14.1, 12.4; IR (neat): 2965 (C=CH₂), 1646 (C=C) (cm⁻¹).

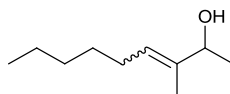
2,2-Dimethyl-3-methyleneundecane **222c**³⁵⁶



A slight variation of General Procedure E was employed. Following the addition of a THF solution of 2,2-dimethyl-3-undecanone (**221c**, 2.80 g) to the phosphorus ylide, the reaction mixture was first stirred at 0 °C for 30 minutes and then refluxed overnight (~16 h). After cooling to room temperature, the reaction mixture was worked up as described in the General Procedure. The solvent was then evaporated under reduced pressure and the residue purified by column chromatography (SiO₂) to afford the title compound as a colourless oil (1.25 g, 45%); ¹H NMR (300 MHz, CDCl₃) δ 4.85 (1H, s, C=CH_AH_B), 4.69 (1H, s, C=CH_AH_B), 1.98-2.07 (2H, m, CH₂C), 1.20-1.54 (12H, m, (CH₂)₆), 1.07 (9H, s, C(CH₃)₃), 0.85-0.94 (3H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 158.4, 105.5, 36.2, 31.9, 31.3, 29.9, 29.7, 29.4, 29.4, 29.3, 22.7, 14.1; IR (neat): 2981 (C=CH₂) 1634 (C=C) (cm⁻¹).

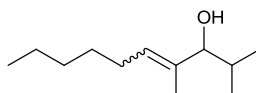
5.5 Palladium-catalysed isomerisation reactions

3-Methylnon-3-en-2-ol **199a**³⁵²



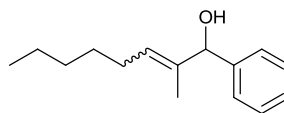
General Procedure F was followed, using 3-methylenenonan-2-ol (**198a**, 0.156 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile at 0 °C, to afford the title compound as a clear oil in 90% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 21:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.33 (1H, t, *J* = 6.2 Hz, C=CH), 4.13 (1H, q, *J* = 6.4 Hz, CH(OH)), 1.88-1.99 (2H, m, CH₂CH=C), 1.53-1.56 (3H, m, CH₃C=CH), 1.14-1.32 (9H, m, CH₃CH(OH) and CH₃(CH₂)₃), 0.82 (3H, t, *J* = 6.8 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 125.8, 73.9, 31.9, 29.6, 27.7, 23.1, 22.0, 21.6, 14.4, 11.8; HRMS (ES): *m/z* [C₁₀H₂₀NaO]⁺ requires 179.1406, found 179.1410.

2,4-Dimethyldec-4-en-3-ol **199b**



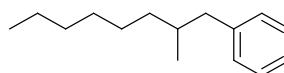
General Procedure F was followed, using 2-methyl-4-methylenedecan-3-ol (**198b**, 0.184 g) and Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) in acetonitrile, to afford the title compound as a clear oil in 96% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 17:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.39 (1H, t, *J* = 6.2 Hz, C=CH), 3.60 (1H, d, *J* = 6.4 Hz, CH(OH)), 1.99-2.11 (2H, m, CH₂CH=C), 1.69-1.90 (1H, m, CH(CH₃)₂), 1.60-1.65 (3H, m, CH₃C=CH), 1.22-1.51 (6H, m, CH₃(CH₂)₃), 1.02 (3H, d, *J* = 3.8 Hz, CH₃CH), 0.85-1.00 (3H, m, CH₃CH₂), 0.79 (3H, d, *J* = 3.6 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 136.6, 128.5, 84.7, 31.9, 31.5, 29.6, 27.8, 22.9, 19.8, 19.1, 14.5, 11.6; HRMS (ES): *m/z* [C₁₀H₂₀NaO]⁺ requires 207.1719, found 207.1732.

2-Methyl-1-phenyloct-2-en-1-ol **199c**



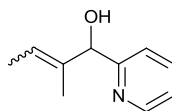
General Procedure F was followed, using 2-methylene-1-phenyloctan-1-ol (**198c**, 0.218 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile, to afford the title compound as a clear oil in 87% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 8:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.14-7.31 (5H, m, Ph), 5.66 (1H, t, *J* = 6.3 Hz, C=CH), 5.05 (1H, s, CH(OH)), 1.95-2.03 (2H, m, CH₂CH=C), 1.39-1.42 (3H, m, CH₃C=CH), 1.09-1.37 (6H, m, CH₃(CH₂)₃), 0.82 (3H, t, *J* = 7.0 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 142.9, 137.0, 128.6, 127.8, 127.6, 126.6, 79.8, 32.0, 29.6, 28.0, 23.0, 14.5, 12.3.

(2-Methyloctyl)benzene **205c**



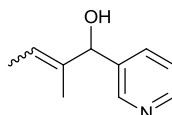
Unoptimised palladium-catalysed isomerisation reactions of 2-methylene-1-phenyloctan-1-ol (**198c**) resulted in the title compound being isolated by column chromatography (SiO₂) as a clear oil in 6 – 22% yields; ¹H NMR (300 MHz, CDCl₃) δ 7.04-7.25 (5H, m, Ph), 2.58 (1H, dd, *J* = 13.1 and 3.9 Hz, PhCH_AH_B), 2.28 (1H, dd, *J* = 13.1 and 8.1 Hz, PhCH_AH_B), 1.58-1.72 (1H, m, CHCH₂Ph), 1.02-1.36 (10H, m, (CH₂)₅), 0.72-0.89 (6H, m, CH₃CH₂ and CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 142.1, 129.6, 128.4, 125.9, 44.1, 37.2, 35.4, 32.3, 30.0, 27.5, 23.1, 19.8, 14.5; IR (neat): 3027 (C–H), 1495 (C=C), 1454 (C=C), 1377 (C=C), (cm⁻¹).

2-Methyl-1-(pyridin-3-yl)but-2-en-1-ol **199d**



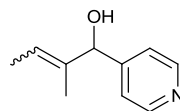
General Procedure F was followed, using 2-methylene-1-(pyridin-3-yl)butan-1-ol (**198d**, 0.161 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in isopropanol, to afford a crude mixture containing the title compound in 27% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 13:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 8.44-8.51 (1H, m, Ar), 7.56-7.67 (1H, m, Ar), 7.08-7.20 (2H, m, Ar), 5.69 (1H, qq, *J* = 6.6 and 1.4 Hz, CH₃CH), 5.03 (1H, s, CH(OH)), 1.62 (3H, dq, *J* = 6.7 and 1.0 Hz, CH₃CH), 1.30-1.33 (3H, m, CH₃C=CH).

2-Methyl-1-(pyridin-3-yl)but-2-en-1-ol **199e**



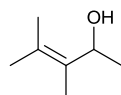
General Procedure F was followed, using 2-methylene-1-(pyridin-3-yl)butan-1-ol (**198e**, 0.161 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in isopropanol, to afford the title compound as a clear oil in 83% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 10:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 8.35-8.52 (2H, m, Ar), 7.57-7.70 (1H, m, Ar), 7.14-7.24 (1H, m, Ar), 5.67 (1H, q, *J* = 6.7 Hz, CH₃CH), 5.11 (1H, s, CH(OH)), 2.52 (1H, br. s, OH), 1.60 (3H, d, *J* = 6.5 Hz, CH₃CH), 1.42 (3H, s, CH₃C=CH); ¹³C NMR (75 MHz, CDCl₃) δ 148.7, 148.5, 138.3, 137.5, 134.3, 123.6, 122.8, 77.7, 13.6, 11.8.

2-Methyl-1-(pyridin-4-yl)but-2-en-1-ol **199f**



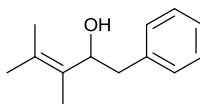
General Procedure F was followed, using 2-methylene-1-(pyridin-4-yl)butan-1-ol (**198f**, 0.161 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in isopropanol, to afford the title compound as a clear oil in 83% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 10:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 8.39-8.47 (2H, m, Ar), 7.20-7.26 (2H, m, Ar), 5.64 (1H, q, *J* = 6.4 Hz, CH₃CH), 5.07 (1H, s, CH(OH)), 2.83 (1H, br. s, OH), 1.60 (3H, d, *J* = 6.4 Hz, CH₃CH), 1.39 (3H, s, CH₃C=CH); ¹³C NMR (75 MHz, CDCl₃) δ 152.1, 149.9, 137.2, 123.9, 121.6, 78.7, 13.6, 11.4.

3,4-Dimethylpent-3-en-2-ol **199g**³⁵³



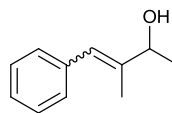
General Procedure F was followed, using 4-methyl-3-methylenepentan-2-ol (**199g**, 0.114 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile, to afford the title compound as a clear oil in 61% yield (determined by ¹H NMR spectroscopy); ¹H NMR (300 MHz, CDCl₃) δ 4.79 (1H, q, *J* = 6.5 Hz, C=CH), 1.65-1.61 (3H, m, CH₃CCH₃), 1.59 (3H, s, CH₃CCH₃), 1.55-1.58 (3H, m, CH₃CCH(OH)), 1.13 (3H, d, *J* = 6.5 Hz, CH₃CH(OH)); ¹³C NMR (75 MHz, CDCl₃) δ 131.0, 126.6, 67.4, 21.5, 21.4, 19.9, 11.7.

3,4-Dimethyl-1-phenylpent-3-en-2-ol **199h**



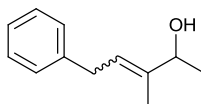
General Procedure F was followed, using 4-methyl-3-methylene-1-phenylpentan-2-ol (**198h**, 0.190 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile, to afford the title compound as a clear oil in 58% yield (determined by ¹H NMR spectroscopy); ¹H NMR (300 MHz, CDCl₃) δ 7.17-7.39 (5H, m, Ph), 4.84 (1H, dd, *J* = 8.1 and 5.7 Hz, CH(OH)), 2.97 (1H, dd, *J* = 13.5 and 3.9 Hz, PhCH_AH_B), 2.88 (1H, dd, *J* = 13.5 and 7.1 Hz, PhCH_AH_B), 1.71-1.76 (3H, m, CH₃CCH₃), 1.66 (3H, s, CH₃CCH₃), 1.3-1.59 (3H, m, CH₃CCH(OH)); ¹³C NMR (75 MHz, CDCl₃) δ 158.8, 139.1, 129.8, 129.0, 128.1, 126.7, 72.8, 41.0, 21.5, 20.0, 12.3.

3-Methyl-4-phenylbut-3-en-2-ol **199i**³⁵⁴



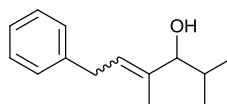
General Procedure F was followed, using 3-benzylbut-3-en-2-ol (**198i**, 0.162 g), Pd(OH)₂/C (8.5% Pd w/w, 0.250 g) and Cs₂CO₃ (0.326 g) in acetonitrile, to afford the title compound as a clear oil in 13% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 2:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.19 (5H, m, Ph), 6.57 (1H, s, PhCH), 4.48 (1H, q, *J* = 6.5 Hz, CHOH), 1.99 (3H, s, CH₃C=CH), 1.46 (3H, d, *J* = 6.5 Hz, CH₃).

3-Methyl-5-phenylpent-3-en-2-ol **199k**³⁵⁵



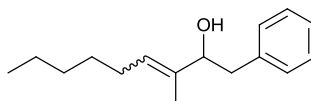
General Procedure F was followed, using 3-methylene-5-phenylpentan-2-ol (**198k**, 0.176 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile at 0 °C, to afford the title compound as a clear oil in 55% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 6:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.15-7.33 (5H, m, Ph), 5.59-5.67 (1H, m, C=CH), 4.27 (1H, q, *J* = 6.4 Hz, CH(OH)), 3.40 (2H, d, *J* = 5.9 Hz, PhCH₂), 1.78 (3H, s, CH₃C=CH), 1.30 (3H, d, *J* = 6.0 Hz, CH₃CH(OH)); ¹³C NMR (75 MHz, CDCl₃) δ 141.5, 140.0, 128.8, 128.7, 126.3, 124.0, 73.7, 34.2, 22.1, 12.1.

2,4-Dimethyl-6-phenylhex-4-en-3-ol **199l**



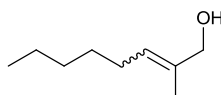
General Procedure F was followed, using 2-methyl-4-methylene-6-phenylhexan-3-ol (**198l**, 0.204 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile, to afford the title compound as a clear oil in 75% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 8:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.13-7.35 (5H, m, Ph), 5.59 (1H, tdq, *J* = 7.1, 1.4 and 0.8 Hz, C=CH), 3.65 (1H, d, *J* = 8.0 Hz, CH(OH)), 3.45 (2H, d, *J* = 5.8 Hz, PhCH₂), 1.71-1.74 (3H, m, CH₃C=CH), 1.44-1.54 (1H, m, CH(CH₃)₂), 1.01 (3H, d, *J* = 6.7 Hz, CH₃CH), 0.84 (3H, d, *J* = 6.8 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 143.3, 141.5, 138.0, 128.7, 126.5, 126.3, 77.0, 33.9, 31.6, 19.9, 19.0, 11.9; HRMS (ES): *m/z* [C₁₄H₂₀NaO]⁺ requires 227.1406, found 227.1390.

3-Methyl-1-phenylnon-3-en-2-ol **199m**



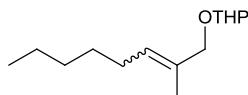
General Procedure F was followed, using 3-methylene-1-phenylnon-2-ol (**198m**, 0.232 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile at 0 °C, to afford the title compound as a clear oil in 80% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 7:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.18-7.35 (5H, m, Ph), 5.41-5.33 (1H, m, C=CH), 4.23 (1H, dd, *J* = 7.6 and 5.7 Hz, CH(OH)), 2.78-2.88 (2H, m, PhCH₂), 2.06-1.96 (2H, m, CH₂CH=C), 1.72-1.69 (3H, m, CH₃C=CH), 1.39-1.16 (6H, m, CH₃(CH₂)₃), 0.89 (3H, t, *J* = 7.0 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 139.0, 136.5, 129.7, 128.9, 127.6, 126.7, 79.0, 42.5, 31.9, 29.5, 27.9, 23.0, 14.4, 12.2.

2-Methyloct-2-en-1-ol **199n**³⁵⁶



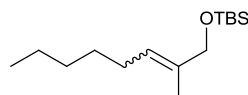
General Procedure F was followed, using 2-methyleneoctan-1-ol (**198n**, 0.142 g), Pd(OH)₂/C (8.5% Pd w/w, 0.188 g) and Cs₂CO₃ (0.326 g) in acetonitrile, to afford the title compound as a clear oil in 65% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 4:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.35 (1H, t, *J* = 6.4 Hz, C=CH), 3.93 (2H, s, CH₂(OH)), 1.89-2.02 (2H, m, CH₂CH=C), 1.57-1.61 (3H, m, CH₃C=CH), 1.14-1.35 (6H, m, CH₃(CH₂)₃), 0.81 (3H, t, *J* = 5.5 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 134.9, 127.1, 69.5, 33.5, 30.9, 28.0, 23.0, 14.5, 14.4; HRMS (ES): *m/z* [C₁₀H₂₀NaO]⁺ requires 165.1250, found 165.1245.

2-((2-Methyloct-2-en-1-yl)oxy)tetrahydro-2H-pyran **199o**



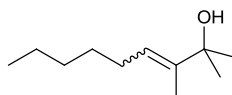
General Procedure F was followed, using 2-((2-methyleneoctyl)oxy)tetrahydro-2H-pyran (**198o**, 0.226 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile at 0 °C, to afford the title compound as a clear oil in 70% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 4:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.39 (1H, t, CH=C, *J* = 6.2 Hz), 4.44-4.59 (1H, m, OCHO), 3.99-4.10 (1H, m, CH₂CH_AH_BO), 3.88-3.75 (2H, m, CCH₂O), 3.35-3.56 (1H, m, CH₂CH_AH_BO), 1.91-2.05 (2H, m, CH₂CH=C), 1.12-1.89 (15H, m, CH₃(CH₂)₃, OCH₂(CH₂)₃ and CH₃C), 0.72-0.85 (3H, m, CH₃CH₂).

tert-Butyldimethyl((2-methyloct-2-en-1-yl)oxy)silane **199p**



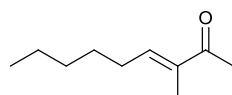
General Procedure F was followed, using *tert*-butyldimethyl((2-methyleneoctyl)oxy)silane (**198p**, 0.257 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in ethyl acetate, to afford the title compound as a clear oil in 70% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 4:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.33 (1H, tq, *J* = 7.2 and 1.4 Hz, CH=C), 3.95 (2H, s, CH₂O), 1.88-2.01 (2H, m, CH₂CH), 1.53 (3H, m, CH₃C=CH), 1.14-1.33 (6H, m, CH₃(CH₂)₃), 0.75-0.89 (3H, m, CH₃CH₂), 0.84 (9H, s, C(CH₃)₃), 0.00 (6H, s, Si(CH₃)₂).

2,3-Dimethylnon-3-en-2-ol **199q**



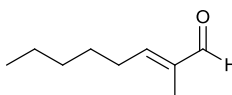
General Procedure F was followed, using 2-methyl-3-methylenenonan-2-ol (**198q**, 0.170 g), Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) and Cs₂CO₃ (0.326 g) in acetonitrile, to afford a crude mixture containing the title compound in 36% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 3:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.51 (1H, t, *J* = 6.2 Hz, C=CH), 1.98-2.06 (2H, m, CH₂=CH), 1.64-1.70 (3H, m, CH₃C=CH), 1.19-1.47 (6H, m, CH₃(CH₂)₃), 1.31 (6H, s, C(CH₃)₂), 0.86-0.97 (3H, m, CH₃CH₂).

(*E*)-3-Methylnon-3-en-2-one **202a**³⁵²



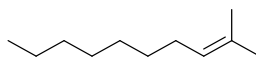
General Procedure F was followed, using 3-methylenenonan-2-one (**201a**, 0.154 g) and Pd(OAc)₂ (0.022 g) in acetonitrile, to afford a crude mixture containing the title compound in 46% yield; ¹H NMR (300 MHz, CDCl₃) δ 6.68 (1H, t, *J* = 7.0 Hz, C=CH), 2.39 (3H, s, CH₃CO), 2.20-2.28 (2H, m, CH₂CH), 1.79 (3H, s, CH₃C), 1.45-1.20 (6H, m, CH₃(CH₂)₃), 0.94-0.80 (3H, m, CH₃CH₂).

(*E*)-2-Methyloct-2-enal **218**³⁵⁷



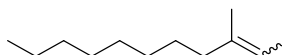
General procedure F was followed, using 2-methyleneoctanal (**197**, 0.140 g) and Pd(OAc)₂ (0.022 g) in acetonitrile, to afford a crude mixture containing the title compound in 9% yield; ¹H NMR (300 MHz, CDCl₃) δ 9.35 (1H, s, CHO), 6.34 (1H, t, *J* = 7.0 Hz, C=CH), 2.14-2.22 (2H, m, CH₂CH), 1.82 (3H, s, CH₃C), 1.18-1.47 (6H, m, (CH₂)₃), 0.88-0.79 (3H, m, CH₃).

2-Methyldec-2-ene **223a**³⁵⁸



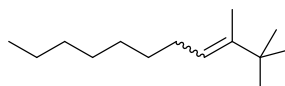
General Procedure F was followed, using 2-methyldec-1-ene (**222a**, 0.154 g) and Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) in isopropanol, to afford the title compound as a clear oil in 63% yield (determined by ¹H NMR spectroscopy); ¹H NMR (300 MHz, CDCl₃) δ 5.09 (1H, t, *J* = 14.0 Hz), 1.84-1.93 (2H, m, CH₂C), 1.61 (3H, s, CH₃C), 1.56 (3H, s, CH₃C), 1.08-1.32 (10H, m, (CH₂)₅), 0.77-0.89 (3H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 131.1, 125.0, 31.9, 29.9, 29.3, 29.3, 28.1, 25.7, 22.7, 17.7, 14.1.

3-Methylundec-2-ene **223b**



General Procedure F was followed, using 3-methyleneundecane (**222b**, 0.168 g) and Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) in isopropanol, to afford the title compound as a clear oil in 36% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 1.6:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.15 (1H, q, *J* = 5.0 Hz, CH₃=CH), 2.32-2.41 (2H, m, CH₂C=CH), 1.84-2.00 (3H, m, CH₃CH), 1.51 (3H, s, CH₃C), 1.10-1.39 (12H, m, (CH₂)₆), 1.03 (3H, t, *J* = 7.5 Hz, CH₃CH₂), 0.75-0.89 (3H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 136.5, 118.6, 32.0, 31.9, 29.6, 29.6, 29.4, 27.9, 23.4, 22.7, 14.2, 13.3.

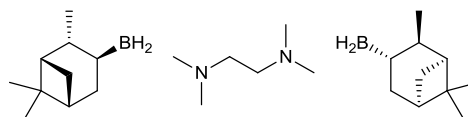
2,2,3-Trimethylundec-3-ene **223c**



General Procedure F was followed, using 2,2-dimethyl-3-methyleneundecane (**222b**, 0.196 g) and Pd(OH)₂/C (8.5% Pd w/w, 0.125 g) in isopropanol, to afford the title compound as a clear oil in 45% yield (determined by ¹H NMR spectroscopy); (*E*):(*Z*) ratio = 9:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 5.11 (1H, t, *J* = 5.2 Hz, CH=C), 1.86-2.01 (2H, m, CH₂CH), 1.53 (3H, s, CH₃C=CH), 1.14-1.49 (10H, m, (CH₂)₅), 0.98 (9H, s, C(CH₃)₃), 0.81-0.90 (3H, m, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 142.9, 121.2, 43.0, 33.0, 31.9, 29.9, 29.8, 29.1, 28.6, 28.2, 25.7, 15.6.

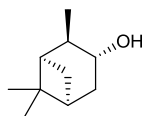
5.6 Preparation of (–)-monoisopinocampheylborane-TMEDA complex

2IpcBH₂.TMEDA 257



According to a literature procedure,³⁰⁶ 33.0 ml dry ether and 5.17 ml (52 mmol approx.) neat borane-methyl sulphide were placed into a two-necked 250 ml round bottom flask, fitted with a condenser. To the stirred mixture was added 18.4 ml (115 mmol) (+)- α -pinene (Aldrich, 91% ee) at a rate sufficient to maintain a gentle reflux. After the addition was complete, the reaction mixture was refluxed (external temperature 45 °C) for an additional 30 m, then the flask was removed from the oil bath and allowed to cool to room temperature while stirring was continued. Following the dropwise addition of 3.77 ml (25 mmol) TMEDA, the solution was refluxed for a further 30 m, the stirring discontinued and the mixture was allowed to cool to room temperature. Crystallisation could be induced by inserting a needle into the solution, withdrawing a couple of millilitres and squirting it back in rapidly, then allowing the solution to stand undisturbed at room temperature, under nitrogen. When crystallisation was clearly underway the solution was refrigerated overnight, then filtered (in a fume cupboard) and washed thoroughly with freezer-cold pentane, to afford 2IpcBH₂.TMEDA as a white solid (4.0 g, 70%); $[\alpha]_D^{26} +60.90$ (c 1.02, THF); lit. value: $[\alpha]_D^{23} +69.03$ (c 9.33, THF);³⁰⁶ ^{11}B NMR (96 MHz, CDCl₃) δ 4.35 (br. s); ^1H NMR (300 MHz, CDCl₃) δ 3.06-3.33 (4H, m, NCH₂CH₂N), 2.62 (6H, s, NCH₃), 2.59 (6H, s, NCH₃), 2.14-2.26 (2H, m, CH_AH_BCHB), 2.00-2.13 (2H, m, CH_AH_BCHB), 1.68-1.89 (10H, m, CHCH₂CH and CHCH₃), 1.48-1.62 (4H, m, BH₂), 1.15 (6H, s, CH₃CCH₃), 1.08 (6H, s, CH₃CCH₃), 0.99 (6H, d, $J = 7.0$ Hz, CH₃CH), 0.58-0.72 (2H, m, CHB); ^{13}C NMR (75 MHz, CDCl₃) δ 57.2, 51.0, 50.8, 48.6, 43.0, 42.3, 39.0, 38.0, 34.1, 28.4, 22.9, 22.7; IR (neat): 2888 (C–H), 1459 (B–C), 1340 (C–N), 1105 (B–N), 1074 (B–H) (cm^{–1}).

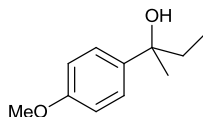
(1*R*,2*R*,3*R*,5*S*)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-ol 258³⁵⁹



To a solution of 2IpcBH₂.TMEDA **257** (0.416 g, 1.0 equiv.) in dry THF (2.0 ml) was added BF₃.OEt₂ (0.278 g, 0.24 ml, 1.96 equiv.) dropwise, and the resulting mixture was stirred at room temperature for 3 hours. The liberated monoalkylborane was treated with aqueous 3.0 M NaOH solution (0.7 ml) and 30% aqueous hydrogen peroxide (0.55 ml), heated to 55 °C for 1 hour and then cooled to room temperature. Ether (10 ml) and water (10 ml) were added to the flask and the resulting mixture was transferred to a separatory funnel. The aqueous phase was subsequently extracted with ether (3 × 10 ml) and the combined organics washed with water (20 ml), dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a white solid (0.302 g, 96%); ¹H NMR (300 MHz, CDCl₃) δ 4.02-4.11 (1H, m, CH(OH)), 2.45-2.58 (1H, m, CH_AH_BCH(OH)), 2.32-2.42 (1H, m, CH_AH_BCH(OH)), 1.86-2.01 (2H, m, CHC(CH₃)₂CH), 1.80 (1H, app. td, *J* = 6.0 and 1.9 Hz, CHCH₃), 1.65-1.76 (2H, m, CHCH₂CH), 1.22 (3H, s, CH₃CCH₃), 1.13 (3H, d, *J* = 7.3 Hz, CHCH₃), 0.92 (3H, s, CH₃CCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 71.7, 47.9, 47.8, 41.8, 39.1, 38.2, 34.4, 27.7, 23.7, 20.7.

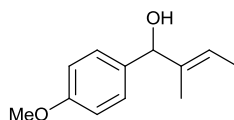
5.7 Synthesis and asymmetric hydroboration reactions of alkene (Z)-245

2-(4-Methoxyphenyl)butan-2-ol **244**³⁶⁰



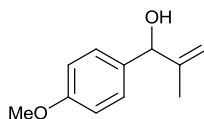
A 0.5 M solution of EtMgBr in ether (16.64 mmol, prepared *via* dilution of the commercially available reagent) was cooled to 0 °C, followed by the dropwise addition of 4'-methoxyacetophenone (1.00 g, 6.66 mmol). The resulting mixture was stirred overnight, whilst slowly warming to room temperature, and then quenched by the cautious addition of saturated NH₄Cl solution. Additional water and 1.0 M HCl were added to dissolve the precipitated salts and the mixture was transferred to a separatory funnel. The organic phase was removed and the aqueous layer extracted with ether (3 × 10 ml). The combined organics were washed with saturated NaHCO₃ solution and water, dried (MgSO₄) and the solvent removed under reduced pressure to afford the title compound as a colourless oil (1.12 g, 93%) which was used in the next step without further purification; ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.40 (2H, m, Ar), 6.85-6.92 (2H, m, Ar), 3.82 (3H, s, OMe), 1.83 (2H, qd, *J* = 7.5 and 2.6 Hz, CH₃CH₂), 1.70 (1H, br. s, OH), 1.54 (3H, s, CH₃C), 0.80 (3H, t, *J* = 7.5 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 158.2, 139.9, 126.1, 113.4, 74.7, 55.2, 36.7, 29.6, 8.4.

(E)-1-(4-Methoxyphenyl)-2-methylbut-2-en-1-ol (E)-246



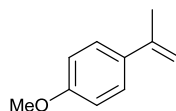
According to a modified literature procedure,³¹² 4-methoxy-1-bromobenzene (39.6 mmol), dry THF (15 ml) and dry toluene (60 ml) were added to a round bottomed flask and the resulting mixture cooled to -78°C . *n*-BuLi solution (2.5 M in hexanes, 15 ml, 37.5 mmol) was then added dropwise and stirring continued at this temperature for four hours. Tiglic aldehyde (2-methyl-but-2-enal, 43.6 mmol) was then added dropwise and the reaction mixture left in the cooling bath overnight, thus warming slowly to room temperature. The reaction was quenched by the addition of 50% saturated aqueous NH_4Cl solution, the organic layer separated and the aqueous fraction extracted with ether (3×50 ml). The combined organics were washed with water, dried (MgSO_4) and the solvent evaporated under reduced pressure to afford a residue which was purified by column chromatography (SiO_2) to afford the title compound as a colourless oil (4.49 g, 59%); ^1H NMR (300 MHz, CDCl_3) δ 7.24-7.31 (2H, m, Ar), 6.85-6.91 (2H, m, Ar), 5.71 (q app. pentets, $J = 6.7$ and 1.3 Hz, $\text{C}=\text{CHMe}$), 5.09 (1H, s, $\text{CH}(\text{OH})$), 3.81 (3H, s, OMe), 1.65-1.70 (3H, m, CH_3CH), 1.48-1.51 (3H, m, CH_3C); ^{13}C NMR (75 MHz, CDCl_3) δ 158.8, 137.7, 134.7, 127.5, 120.7, 113.6, 78.9, 55.3, 13.2, 11.9; IR (neat): 3409 (O–H), 1611 (C=C), 1509 (C=C), 1244 (C–O), 1170 (C–O) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{12}\text{H}_{16}\text{NaO}_2]^+$ requires 215.1048, found 215.1032.

(Z)-1-(4-Methoxyphenyl)-2-methylbut-2-en-1-ol (Z)-246



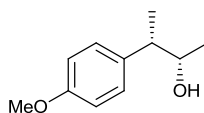
Allylic alcohol (Z)-**246** was also isolated from the above reaction (0.23 g, 3%); ^1H NMR (300 MHz, CDCl_3) δ 7.20-7.26 (2H, m, Ar), 6.83-6.92 (2H, m, Ar), 6.38 (1H, s, $\text{CH}(\text{OH})$), 4.38 (1H, q, $J = 6.4$ Hz, CH_3CH), 3.82 (3H, s, OMe), 1.89 (3H, d, $J = 1.3$ Hz, CH_3C), 1.37 (3H, d, $J = 6.4$ Hz, CH_3CH); ^{13}C NMR (75 MHz, CDCl_3) δ 158.1, 140.0, 130.2, 130.2, 124.0, 113.6, 73.9, 55.3, 21.8, 13.3; IR (neat): 3376 (O-H), 1607 (C=C), 1509 (C=C), 1245 (C-O), 1176 (C-O) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{12}\text{H}_{16}\text{NaO}_2]^+$ requires 215.1048, found 215.1036.

(Z)-1-(But-2-en-2-yl)-4-methoxybenzene (Z)-245³¹³



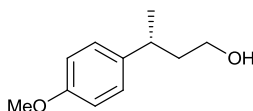
According to a literature procedure,³¹³ allylic alcohol (E)-**246** (1.92 g, 10 mmol) was dissolved in dry DME (20 ml) and to this solution was added NBS (2.14 g, 12 mmol), in one portion. The resulting mixture was stirred at room temperature until tlc analysis indicated complete consumption of the alcohol. Following the addition of a further 10 ml of dry DME, solid NaOH powder (10.0 g, 250 mmol) was then added to the reaction mixture, in small portions, under vigorous stirring. Stirring was subsequently continued for 24 hours, whereupon the reaction mixture was diluted with water (50 ml) and thoroughly extracted with ether (5 \times 40 ml). The combined organic extracts were washed with water, dried (MgSO_4) and the solvent evaporated under reduced pressure to afford the title compound as a clear oil (1.04 g, 64%) which was used without further purification; ^1H NMR (300 MHz, CDCl_3) δ 7.13-7.19 (2H, m, Ar), 6.87-6.93 (2H, Ar, m), 5.55 (1H, qq, $J = 6.9$ and 1.5 Hz, CH_3CH), 3.83 (3H, s, OMe), 2.02 (3H, app. pentet, $J = 1.5$ Hz, CH_3C), 1.63 (3H, dq, $J = 6.9$ and 1.5 Hz, CH_3CH); ^{13}C NMR (75 MHz, CDCl_3) δ 158.1, 136.2, 134.2, 129.2, 121.1, 113.4, 55.2, 25.5, 14.9; IR (neat): 1609 (C=C), 1509 (C=C), 1244 (C-O) cm^{-1} .

(–)-(2*S*,3*S*)-3-(4-Methoxyphenyl)butan-2-ol 247³⁶¹



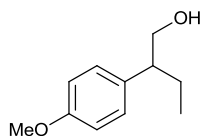
(*Z*)-1-(But-2-en-2-yl)-4-methoxybenzene (**245**, 0.324 g) was treated according to General Procedure G and the title compound isolated by column chromatography (SiO₂) in 54% yield (0.195 g) and >99% ee, which was determined by chiral HPLC (OD-H, 0.3 ml/min, 95:5 hexane-IPA, 215 nm, $t_{\text{major}} = 28.443$, $t_{\text{minor}} = 29.060$); $[\alpha]_{\text{D}}^{26} -6.19$ (c 0.49, EtOH); ¹H NMR (300 MHz, CDCl₃) δ 7.10-7.17 (2H, m, Ar), 6.84-6.90 (2H, m, Ar), 3.85 (1H, app. pentet, $J = 6.2$ Hz, CH₃CH(OH)), 3.81 (3H, s, OMe), 2.71 (1H, app. pentet, $J = 6.8$ Hz, ArCH), 1.49 (1H, br. s, OH), 1.31 (3H, d, $J = 7.0$ Hz, ArCHCH₃), 1.09 (3H, d, $J = 6.3$ Hz, CH₃CH(OH)); ¹³C NMR (75 MHz, CDCl₃) δ 158.2, 136.2, 128.7, 113.8, 72.5, 72.5, 46.2, 20.9, 16.1.

(–)-(3*R*)-3-(4-Methoxyphenyl)butan-1-ol 249³⁶²



(*Z*)-1-(But-2-en-2-yl)-4-methoxybenzene (**245**, 0.324 g) was treated according to General Procedure H and the title compound isolated by column chromatography (SiO₂) in 34% yield (0.123 g) and 5% ee, which was determined by chiral HPLC (OD-H, 0.5 ml/min, 95:5 hexane-IPA, 215 nm, $t_{\text{major}} = 27.877$, $t_{\text{minor}} = 29.570$); $[\alpha]_{\text{D}}^{26} -0.60$ (c 0.54, EtOH); lit. value for epimer: $[\alpha]_{\text{D}}^{20} +11.60$ (c 0.5, CHCl₃);³⁶³ ¹H NMR (300 MHz, CDCl₃) δ 7.10-7.17 (2H, m, Ar), 6.82-6.89 (2H, m, Ar), 3.80 (3H, s, OMe), 3.49-3.64 (2H, m, CH₂OH), 2.78-2.92 (1H, m, CH₃CH), 1.78-1.88 (2H, m, CH₂CH₂OH), 1.40 (1H, br. s, OH), 1.26 (3H, d, $J = 7.0$ Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 157.9, 138.9, 127.8, 113.9, 61.3, 55.3, 41.2, 35.7, 22.7.

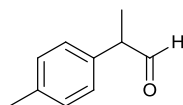
2-(4-Methoxyphenyl)butan-1-ol 250³⁶⁴



The title compound was also isolated from the previously described reaction (0.043 g, 12%); ¹H NMR (300 MHz, CDCl₃) δ 7.11-7.17 (2H, m, Ar), 6.86-6.92 (2H, m, Ar), 3.81 (3H, s, OMe), 3.76 (1H, dd, *J* = 10.7 and 5.8 Hz, CH_AH_B(OH)), 3.68 (1H, dd, *J* = 10.7 and 8.0 Hz, CH_AH_B(OH)), 2.56-2.77 (1H, m, CH₂CH), 1.65-1.81 (1H, m, CH₃CH_AH_B), 1.48-1.63 (1H, m, CH₃CH_AH_B), 0.84 (3H, t, *J* = 7.3 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 158.4, 134.1, 129.0, 114.1, 67.5, 55.3, 49.7, 25.1, 12.0.

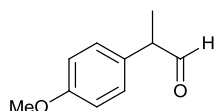
5.8 Synthesis of 2-arylpropionaldehydes

2-(*p*-Tolyl)propanal **273b**³⁶⁵



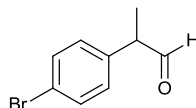
4'-Methylacetophenone (**272b**, 37.45 mmol, 5.025 g, 5.0 ml) was treated according to General Procedure I to afford the title compound as a colourless oil (3.33 g, 60%); ¹H NMR (300 MHz, CDCl₃) δ 9.67 (1H, d, *J* = 1.4 Hz, CHO), 7.20 (2H, d, *J* = 8.1 Hz, Ar), 7.10 (2H, d, *J* = 8.1 Hz, Ar), 3.60 (1H, qd, *J* = 7.0 and 1.2 Hz, CHCH₃), 2.35 (3H, s, ArCH₃), 1.43 (3H, d, *J* = 7.0 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 201.2, 137.3, 134.7, 129.8, 128.2, 52.6, 21.1, 14.6; IR (neat): 1722 (C=O) cm⁻¹; HRMS (ES): *m/z* [C₁₀H₁₂NaO]⁺ requires 171.0786, found 171.0800.

2-(4-Methoxyphenyl)propanal **273c**³⁶⁶



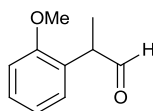
4'-Methoxyacetophenone (**272c**, 33.3 mmol, 5.00 g) was treated according to General Procedure I to afford the title compound as a colourless oil (2.84 g, 52%); ¹H NMR (300 MHz, CDCl₃) δ 9.65 (1H, d, *J* = 1.5 Hz, CHO), 7.11-7.17 (2H, m, Ar), 6.89-6.95 (2H, m, Ar), 3.81 (3H, s, OCH₃), 3.59 (1H, qd, *J* = 7.0 and 1.5 Hz, CHCH₃), 1.42 (3H, d, *J* = 7.0 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 201.2, 159.0, 129.6, 129.4, 114.5, 55.3, 52.1, 14.7; IR (neat): 1717 (C=O) cm⁻¹; HRMS (ES): *m/z* [C₁₀H₁₂NaO₂]⁺ requires 187.0735, found 187.0743.

2-(4-Bromophenyl)propanal **273d**³⁶⁶



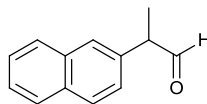
4'-Bromoacetophenone (**272d**, 25.1 mmol, 5.00 g) was treated according to General Procedure I to afford the title compound as a clear yellow oil (3.21 g, 60%); ¹H NMR (300 MHz, CDCl₃) δ 9.67 (1H, d, *J* = 1.2 Hz, CHO), 7.48-7.54 (2H, m, Ar), 7.07-7.13 (2H, m, Ar), 3.62 (1H, qd, *J* = 7.2 and 1.2 Hz, CHCH₃), 1.44 (3H, d, *J* = 7.2 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 200.4, 136.7, 132.2, 130.0, 121.6, 52.4, 14.6; IR (neat): 1723 (C=O) cm⁻¹.

2-(2-Methoxyphenyl)propanal **273e**³⁶⁷



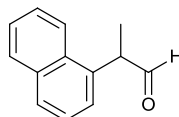
2'-Methoxyacetophenone (**272e**, 36.3 mmol, 5.045 g, 5.0 ml) was treated according to General Procedure I to afford the title compound as a colourless oil (2.86 g, 48%); ¹H NMR (300 MHz, CDCl₃) δ 9.67 (1H, s, CHO), 7.25-7.33 (1H, m, Ar), 7.12 (1H, dd, *J* = 7.5 and 1.7 Hz, Ar), 6.98 (1H, app. td, *J* = 7.4 and 1.0 Hz, Ar), 6.92 (1H, d, *J* = 8.3 Hz, Ar), 3.87 (1H, q, *J* = 7.1 Hz, CHCH₃), 3.82 (3H, s, OCH₃), 1.39 (3H, d, *J* = 7.1 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 202.1, 157.1, 129.2, 128.7, 127.0, 121.0, 110.8, 55.4, 47.4, 13.4; IR (neat): 1722 (C=O) cm⁻¹; HRMS (ES): *m/z* [C₁₀H₁₂NaO₂]⁺ requires 187.0735, found 187.0738.

2-(Naphthalen-2-yl)propanal **273f**³⁶⁶



2-Acetonaphthone (**272f**, 29.4 mmol, 5.0 g) was treated according to General Procedure I to afford the title compound as a white solid (2.98 g, 55%); ¹H NMR (300 MHz, CDCl₃) δ 9.69 (1H, d, *J* = 1.4 Hz, CHO), 7.71-7.82 (3H, m, Ar), 7.60 (1H, s, Ar), 7.37-7.47 (2H, m, Ar), 7.24 (1H, dd, *J* = 8.4 and 1.8 Hz, Ar), 3.73 (1H, qd, *J* = 7.0 and 1.1 Hz, CHCH₃), 1.46 (3H, d, *J* = 7.0 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 201.1, 135.1, 133.6, 132.7, 128.9, 127.7 (2), 127.2, 126.5, 126.2, 126.2, 53.2, 14.7; IR (neat): 1719 (C=O) cm⁻¹; HRMS (ES): *m/z* [C₁₃H₁₂NaO]⁺ requires 207.0786, found 207.0805.

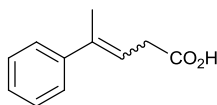
2-(Naphthalen-1-yl)propanal **273g**



1-Acetonaphthone (**272g**, 32.9 mmol, 5.60 g, 5.0 ml) was treated according to General Procedure I to afford the title compound as a colourless oil (2.42 g, 40%); ¹H NMR (300 MHz, CDCl₃) δ 9.77 (1H, d, *J* = 1.0 Hz, CHO), 7.99-8.06 (1H, m, Ar), 7.89-7.95 (1H, m, Ar), 7.80-7.87 (1H, m, Ar), 7.45-7.62 (3H, m, Ar), 7.27-7.34 (1H, m, Ar), 4.39 (1H, qd, *J* = 7.0 and 1.0 Hz, CHCH₃), 1.59 (3H, d, *J* = 7.0 Hz, CH₃CH); ¹³C NMR (75 MHz, CDCl₃) δ 201.3, 134.2, 134.2, 131.8, 129.2, 128.3, 126.7, 126.0, 125.7, 125.7, 123.0, 48.9, 14.7; IR (neat): 1720 (C=O) cm⁻¹; HRMS (ES): *m/z* [C₁₃H₁₂NaO]⁺ requires 207.0786, found 207.0783.

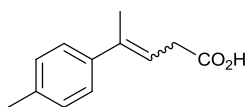
5.9 Synthesis of 4-arylpent-3-enoic acids

4-Phenylpent-3-enoic acid **274a**³²⁵



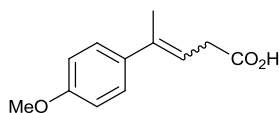
2-Phenylpropionaldehyde (149.4 mmol, 20.04 g, 20.0 ml) was treated according to General Procedure J to afford the title compound as a highly aromatic, waxy white solid (10.27 g, 39%); (*E*):(*Z*) ~15:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.15-7.44 (5H, m, Ph), 5.94 (1H, t, *J* = 7.2 Hz, C=CH), 3.32 (2H, d, *J* = 7.2 Hz, CHCH₂), 2.08 (3H, s, Me); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 142.9, 138.7, 128.3, 127.7, 125.8, 118.4, 34.2, 16.3; IR (neat): 2951 (O–H), 1695 (C=O) cm⁻¹.

4-(*p*-Tolyl)pent-3-enoic acid **274b**



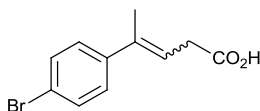
2-(*p*-Tolyl)propanal (**273b**, 3.30 g, 22.3 mmol) was treated according to General Procedure J to afford the title compound as a waxy white solid (1.82 g, 43%); (*E*):(*Z*) ~10:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.30 (2H, d, *J* = 8.0 Hz, Ar), 7.10 (2H, d, *J* = 8.0 Hz, Ar), 5.90 (1H, t, *J* = 7.3 Hz, CHCH₂), 3.30 (2H, d, *J* = 7.3 Hz, CHCH₂), 2.34 (3H, s, ArCH₃), 2.05 (3H, s, CH₃CAr); ¹³C NMR (75 MHz, CDCl₃) δ 177.9, 140.0, 138.5, 136.9, 129.0, 125.7, 117.5, 34.1, 21.1, 16.3.

4-(4-Methoxyphenyl)pent-3-enoic acid **274c**³²⁵



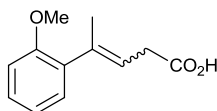
2-(4-Methoxyphenyl)propanal (**273c**, 2.80 g, 17.1 mmol) was treated according to General Procedure J to afford the title compound as a waxy white solid (1.20 g, 34%); (*E*):(*Z*) ~10:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.39 (2H, m, Ar), 6.83-6.91 (2H, m, Ar), 5.87 (1H, tq, *J* = 7.2 and 1.3 Hz, CHCH₂), 3.82 (3H, s, OCH₃), 3.30 (2H, d, *J* = 7.2 Hz, CHCH₂), 2.04-2.07 (3H, m, CH₃C); ¹³C NMR (75 MHz, CDCl₃) δ 178.3, 158.9, 138.0, 135.4, 128.7, 116.8, 113.6, 55.3, 34.2, 16.3.

4-(4-Bromophenyl)pent-3-enoic acid **274d**



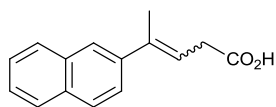
2-(4-Bromophenyl)propanal (**273d**, 3.10 g, 14.5 mmol) was treated according to General Procedure J to afford the title compound as a waxy white solid (1.22 g, 33%); (*E*):(*Z*) ~7:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.48 (2H, m, Ar), 7.25-7.30 (2H, m, Ar), 5.93 (1H, tq, *J* = 7.1 and 1.2 Hz, CHCH₂), 3.31 (2H, dd, *J* = 7.1 and 0.6 Hz, CHCH₂), 2.05 (3H, d, *J* = 1.2 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 177.6, 141.7, 137.7, 131.3, 127.5, 121.2, 119.0, 34.0, 16.2.

4-(2-Methoxyphenyl)pent-3-enoic acid **274e**



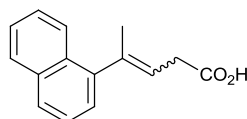
2-(2-Methoxyphenyl)propanal (**273e**, 2.80 g, 17.1 mmol) was treated according to General Procedure J to afford the title compound as a waxy white solid (1.23 g, 35%); (*E*):(*Z*) ~5:1; (*E*)-isomer: ¹H NMR (300 MHz, CDCl₃) δ 7.13-7.30 (2H, m, Ar), 6.83-7.01 (2H, m, Ar), 5.66 (1H, tq, *J* = 7.0 and 1.4 Hz, CHCH₂), 3.61 (3H, s, OMe), 3.10 (2H, dd, *J* = 7.0 and 0.6 Hz, CHCH₂), 1.79-1.82 (3H, m, CH₃C); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 156.5, 139.0, 133.8, 129.7, 128.1, 120.6, 120.1, 110.7, 55.3, 33.8, 17.5.

4-(Naphthalen-2-yl)pent-3-enoic acid **274f**



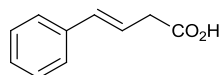
2-(Naphthalen-2-yl)propanal (**273f**, 2.90 g, 15.7 mmol) was treated according to General Procedure J to afford the title compound as a waxy white solid (1.64 g, 46%); (*E*):(*Z*) ~8:1; (*E*)-isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.77-7.89 (4H, m, Ar), 7.61 (1H, dd, J = 8.6 and 1.8 Hz, Ar), 7.44-7.50 (2H, m, Ar), 6.12 (1H, tq, J = 7.1 and 1.4 Hz, CHCH_2), 3.39 (2H, dd, J = 7.1 and 0.8 Hz, CHCH_2), 2.18-2.21 (3H, m, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 178.6, 140.1, 138.6, 133.4, 132.7, 128.2, 127.8, 127.5, 126.2, 126.0, 125.8, 124.5, 124.3, 34.3, 16.3.

4-(Naphthalen-1-yl)pent-3-enoic acid **274g**



2-(Naphthalen-1-yl)propanal (**273g**, 2.40 g, 13.0 mmol) was treated according to General Procedure J to afford the title compound as a waxy white solid (1.00 g, 34%); (*E*):(*Z*) ~4:1; (*E*)-isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.93-8.02 (1H, m, Ar), 7.71-7.91 (2H, m, Ar), 7.38-7.53 (3H, m, Ar), 7.23-7.33 (1H, m, Ar), 5.71 (1H, t, J = 7.2 Hz, CHCH_2), 3.41 (2H, d, J = 7.2 Hz, CHCH_2), 2.14 (3H, s, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 178.1, 142.9, 139.4, 133.8, 131.1, 128.3, 127.3, 125.9, 125.7, 125.4, 125.1, 124.9, 121.2, 34.5, 19.4.

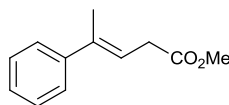
(*E*)-4-Phenylbut-3-enoic acid **274h**³⁶⁸



Phenylacetaldehyde (42.7 mmol, 5.14 g, 5.0 ml) was treated according to General Procedure J to afford the title compound as a colourless oil (3.88 g, 56%); ^1H NMR (300 MHz, CDCl_3) δ 7.12-7.48 (5H, m, Ph), 6.53 (1H, d, J = 16.0 Hz, PhCH), 6.30 (1H, dt, J = 16.0 and 7.1 Hz, PhCH=CH), 3.31 (2H, dd, J = 7.1 and 1.4 Hz, CH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 177.8, 136.7, 134.0, 128.6, 127.7, 126.4, 120.9, 38.0.

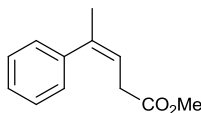
5.10 Synthesis of methyl 4-arylpent-3-enoate esters

(*E*)-Methyl 4-phenylpent-3-enoate (*E*)-275a³⁶⁹



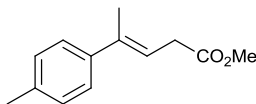
4-Phenylpent-3-enoic acid (**274a**, 10.0 g, 56.8 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (8.31 g, 77%); ¹H NMR (300 MHz, CDCl₃) δ 7.21-7.44 (5H, m, Ph), 5.95 (1H, tq, *J* = 7.1 and 1.4 Hz, CHCH₂), 3.72 (3H, s, OCH₃), 3.27 (2H, d, *J* = 7.1 Hz, CH₂), 2.05-2.08 (3H, m, CH₃C); ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 143.1, 138.1, 128.3, 127.1, 125.8, 119.2, 52.0, 34.3, 16.2.

(*Z*)-Methyl 4-phenylpent-3-enoate (*Z*)-275a



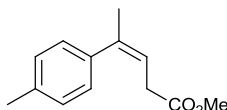
The title compound was also isolated from the above reaction as a colourless oil (0.54 g, 5%); ¹H NMR (300 MHz, CDCl₃) δ 7.13-7.40 (5H, m, Ph), 5.65 (1H, t, *J* = 7.3 Hz, CHCH₂), 3.67 (3H, s, OCH₃), 3.02 (2H, d, *J* = 7.3 Hz, CH₂), 2.08 (3H, s, CH₃C); ¹³C NMR (75 MHz, CDCl₃) δ 172.8, 140.3, 128.3, 127.8, 127.0, 118.4, 51.8, 34.6, 25.6.

(E)-Methyl 4-(*p*-tolyl)pent-3-enoate (E)-275b



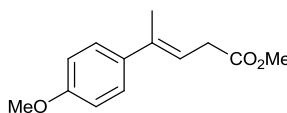
4-(*p*-Tolyl)pent-3-enoic acid (**274b**, 1.80 g, 9.46 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (1.53 g, 79%); ^1H NMR (300 MHz, CDCl_3) δ 7.30 (2H, d, $J = 8.1$ Hz, Ar), 7.13 (2H, d, $J = 8.1$ Hz, Ar), 5.92 (1H, tq, $J = 7.2$ and 1.4 Hz, CHCH_2), 3.72 (3H, s, OCH_3), 3.26 (2H, dd, $J = 7.1$ and 0.6 Hz, CHCH_2), 2.34 (3H, s, CH_3Ar), 2.03-2.06 (3H, m, CH_3CAr); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5, 140.2, 137.9, 136.8, 128.9, 125.7, 118.4, 51.9, 34.3, 21.1, 16.2; IR (neat): 1737 (C=O), 1160 (C–O), 802 (C–H) cm^{-1} ; HRMS (ES): m/z [$\text{C}_{13}\text{H}_{17}\text{O}_2$] $^+$ requires 205.1229, found 205.1242.

(Z)-Methyl 4-(*p*-tolyl)pent-3-enoate (Z)-275b



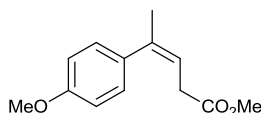
The title compound was also isolated from the above reaction as a colourless oil (0.116 g, 6%); ^1H NMR (300 MHz, CDCl_3) δ 7.17 (2H, d, $J = 8.0$ Hz, Ar), 7.08 (2H, d, $J = 8.0$ Hz, Ar), 5.63 (1H, tq, $J = 7.4$ and 1.5 Hz, CHCH_2), 3.68 (3H, s, OCH_3), 3.04 (2H, dd, $J = 7.4$ and 1.1 Hz, CHCH_2), 2.36 (3H, s, CH_3Ar), 2.06-2.10 (3H, m, CH_3CAr); ^{13}C NMR (75 MHz, CDCl_3) δ 172.9, 140.2, 138.0, 136.7, 129.0, 127.7, 118.1, 51.8, 34.7, 25.7, 21.2.

(E)-Methyl 4-(4-methoxyphenyl)pent-3-enoate (E)-275c



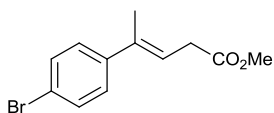
4-(4-Methoxyphenyl)pent-3-enoic acid (**274c**, 1.19 g, 5.57 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (1.02 g, 83%); ^1H NMR (300 MHz, CDCl_3) δ 7.33-7.39 (2H, m, Ar), 6.84-6.90 (2H, m, Ar), 5.89 (1H, tq, J = 7.2 and 1.3 Hz, CHCH_2), 3.81 (3H, s, CH_3OAr), 3.72 (3H, s, CO_2CH_3), 3.26 (2H, d, J = 7.2 Hz, CHCH_2), 2.02-2.06 (3H, m, CH_3CAr); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5, 158.8, 153.4, 137.4, 135.6, 126.9, 117.6, 113.6, 55.3, 51.9, 34.3, 16.2; IR (neat): 1735 (C=O), 1243 (C–O), 1160 (C–O), 821 (C–H) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{13}\text{H}_{17}\text{O}_3]^+$ requires 221.1178, found 221.1203.

(Z)-Methyl 4-(4-methoxyphenyl)pent-3-enoate (Z)-275c



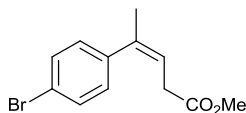
The title compound was also isolated from the above reaction as a colourless oil (0.074 g, 6%); ^1H NMR (300 MHz, CDCl_3) δ 7.10-7.16 (2H, m, Ar), 6.86-6.92 (2H, m, Ar), 5.61 (1H, tq, J = 7.3 and 1.5 Hz, CHCH_2), 3.82 (3H, s, CH_3OAr), 3.68 (3H, s, CO_2CH_3), 3.04 (2H, dd, J = 7.3 and 1.1 Hz, CHCH_2), 2.05-2.08 (3H, m, CH_3CAr); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5, 158.8, 153.4, 137.4, 135.6, 126.9, 117.6, 113.6, 55.3, 51.9, 34.3, 16.2.

(E)-Methyl 4-(4-bromophenyl)pent-3-enoate (E)-275d



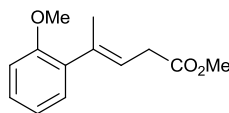
4-(4-Bromophenyl)pent-3-enoic acid (**274d**, 1.20 g, 4.70 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (1.01 g, 80%); ^1H NMR (300 MHz, CDCl_3) δ 7.41-7.47 (2H, m, Ar), 7.25-7.30 (2H, m, Ar), 5.95 (1H, tq, $J = 7.1$ and 1.4 Hz, CHCH_2), 3.73 (3H, s, OCH_3), 3.26 (2H, dd, $J = 7.1$ and 0.8 Hz, CHCH_2), 2.02-2.05 (3H, m, CH_3C); ^{13}C NMR (75 MHz, CDCl_3) δ 172.2, 141.9, 137.1, 131.3, 127.5, 121.0, 119.8, 52.0, 34.3, 16.1; IR (neat): 1735 (C=O), 1163 (C–O), 1076 (C–Br), 807 (C–H) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{12}\text{H}_{13}\text{BrNaO}_2]^+$ requires 290.9997, found 290.9988.

(Z)-Methyl 4-(4-bromophenyl)pent-3-enoate (Z)-275d



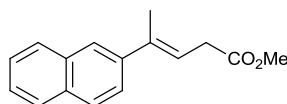
The title compound was also isolated from the above reaction (0.089 g, 7%); ^1H NMR (300 MHz, CDCl_3) δ 7.48 (2H, d, $J = 8.3$ Hz, Ar), 7.06 (2H, d, $J = 8.3$ Hz, Ar), 5.67 (1H, t, $J = 7.3$ Hz, CHCH_2), 3.68 (3H, s, OCH_3), 2.99 (2H, d, $J = 7.3$ Hz, CHCH_2), 2.06 (3H, s, CH_3C); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5, 139.9, 139.2, 131.5, 129.6, 121.0, 119.1, 51.9, 34.6, 25.4; IR (neat): 1736 (C=O), 1164 (C–O), 1075 (C–Br), 835 (C–H) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{12}\text{H}_{13}\text{BrNaO}_2]^+$ requires 290.9997, found 290.9979.

(E)-Methyl 4-(2-methoxyphenyl)pent-3-enoate (E)-275e



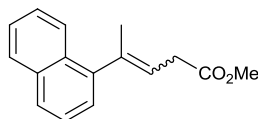
4-(2-Methoxyphenyl)pent-3-enoic acid (**274e**, 1.20 g, 5.82 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (0.718 g, 56%); ^1H NMR (300 MHz, CDCl_3) δ 7.21-7.26 (1H, m, Ar), 7.13-7.18 (1H, m, Ar), 6.91-6.95 (1H, m, Ar), 6.84-6.90 (1H, m, Ar), 5.67 (1H, tq, $J = 7.0$ and 1.4 Hz, CHCH_2), 3.83 (3H, s, CH_3OAr), 3.72 (3H, s, CO_2CH_3), 3.25 (2H, dd, $J = 7.0$ and 0.6 Hz, CHCH_2), 1.99-2.02 (3H, m, CH_3C); ^{13}C NMR (75 MHz, CDCl_3) δ 172.5, 156.6, 138.4, 134.0, 129.7, 128.3, 120.8, 120.6, 110.7, 55.4, 51.8, 34.0, 17.4; IR (neat): 1736 (C=O), 1232 (C–O), 1160 (C–O) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{13}\text{H}_{17}\text{NaO}_3]^+$ requires 221.1178, found 221.1179.

(E)-Methyl 4-(naphthalen-2-yl)pent-3-enoate (E)-275f



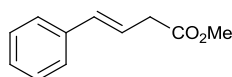
4-(Naphthalen-2-yl)pent-3-enoic acid (**274f**, 1.60 g, 7.07 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (1.26 g, 74%); ^1H NMR (300 MHz, CDCl_3) δ 7.77-7.86 (4H, m, Ar), 7.60 (1H, dd, $J = 8.6$ and 1.8 Hz, Ar), 7.41-7.51 (2H, m, Ar), 6.12 (1H, tq, $J = 7.1$ and 1.4 Hz, CHCH_2), 3.75 (3H, s, OCH_3), 3.34 (2H, dd, $J = 7.1$ and 0.7 Hz, CH_2), 2.17-2.20 (3H, m, CH_3C); ^{13}C NMR (75 MHz, CDCl_3) δ 172.4, 140.2, 138.0, 133.4, 132.6, 128.1, 127.7, 127.5, 126.1, 125.7, 124.4, 124.3, 119.8, 52.0, 34.4, 16.3; IR (neat): 1735 (C=O), 1161 (C–O), 810 (C–H) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{16}\text{H}_{17}\text{O}_2]^+$ requires 241.1229, found 241.1231.

Methyl 4-(naphthalen-1-yl)pent-3-enoate **275g**



4-(Naphthalen-1-yl)pent-3-enoic acid (**274g**, 0.99 g, 4.38 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (0.368 g, 35%); (*E*):(*Z*) = 4:1; (*E*)-isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.94-8.02 (1H, m, Ar), 7.82-7.90 (1H, m, Ar), 7.73-7.80 (1H, m, Ar), 7.45-7.51 (1H, m, Ar), 7.29 (1H, dd, $J = 7.0$ and 1.3 Hz, Ar), 5.72 (1H, tq, $J = 7.2$ and 1.4 Hz, CHCH_2), 3.76 (3H, s, OCH_3), 3.37 (2H, dd, $J = 7.2$ and 0.7 Hz, CH_2), 2.11-2.15 (3H, m, CH_3C); ^{13}C NMR (75 MHz, CDCl_3) δ 172.3, 143.0, 138.8, 133.8, 131.1, 128.3, 127.2, 125.8, 125.8, 125.6, 125.4, 124.9, 121.9, 51.9, 34.1, 19.3; IR (neat): 1735 (C=O), 1162 (C–O), 800 (C–H) cm^{-1} ; HRMS (ES): m/z [$\text{C}_{16}\text{H}_{17}\text{O}_2$] $^+$ requires 241.1229, found 241.1225.

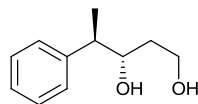
(*E*)-Methyl 4-phenylbut-3-enoate **275h**³⁷⁰



(*E*)-4-Phenylbut-3-enoic acid (**274h**, 3.80 g, 23.4 mmol) was treated according to General Procedure K to afford the title compound as a colourless oil (2.81 g, 68%); ^1H NMR (300 MHz, CDCl_3) δ 7.22-7.41 (5H, m, Ph), 6.50 (1H, d $J = 15.8$ Hz, PhCH), 6.30 (1H, dt, $J = 15.8$ and 7.0 Hz, PhCH=CH), 3.72 (3H, s, OCH_3), 3.26 (2H, d, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 136.8, 133.5, 128.6, 127.6, 126.3, 121.7, 51.9, 38.3.

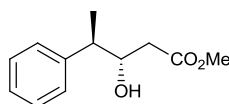
5.11 Asymmetric hydroborations reactions of methyl 4-arylpent-3-enoate esters

(+)-(3*S*,4*R*)-4-Phenylpentane-1,3-diol **277a**³⁷¹



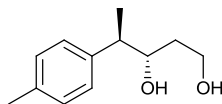
(*E*)-Methyl 4-phenylpent-3-enoate (**275a**, 0.50 g, 2.63 mmol) was treated according to a slight variation on General Procedure L (where the hydroboration reaction was carried out at a temperature of -78 °C to 17 °C, over 42 hours) to afford the title compound as a colourless oil (0.26 g, 55%) in 87% ee, which was determined by General Procedure M; $[\alpha]_D^{26} +6.35$ (c 4.55, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.21-7.38 (5H, m, Ph), 3.77-3.97 (3H, m, CH₂(OH) and CH(OH)), 2.79 (app. p, *J* = 7.0 Hz, CH₃CH), 2.17 (2H, br. s, OH), 1.82-1.95 (1H, m, CH(OH)CH_AH_B), 1.58-1.74 (1H, m, CH(OH)CH_AH_B), 1.28 (3H, d, *J* = 7.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 143.0, 128.8, 128.1, 126.9, 76.8, 61.9, 46.6, 35.6, 17.6; IR (neat): 3350 (O–H), 1048 (C–O) cm⁻¹; HRMS (ES): *m/z* [C₁₁H₁₆NaO₂]⁺ requires 203.1043, found 203.1052

(–)-(3*S*,4*R*)-Methyl 3-hydroxy-4-phenylpentanoate **276a**³⁷⁷



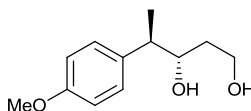
(*E*)-Methyl 4-phenylpent-3-enoate (**275a**, 0.50 g, 2.63 mmol) was treated with two equivalents of (–)-IpcBH₂ according to a slightly modified version of General Procedure L: the solution of (–)-IpcBH₂ obtained upon treatment of 2IpcBH₂.TMEDA with BF₃.OEt₂ was cooled to –25 °C prior to addition of the ester **275a** and the reaction mixture subsequently stirred at this temperature for 48 hours before the excess borane was quenched, at –25 °C, with methanol and the intermediate organoboranes oxidised with NaHCO₃/H₂O₂ to afford a mixture of isopinocampheol **258** and the title compound, which was isolated as a colourless oil (0.246 g, 45%) *via* column chromatography (SiO₂). A sample of the ester was subsequently reduced with LiAlH₄ in an identical manner to that described below for the synthesis of (*E*)-4-phenylpent-3-en-1-ol (**287**) to afford the diol **277a**, whereupon its ee was found to be 75% following application of General Procedure M; $[\alpha]_D^{26}$ –11.66 (c 3.86, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.13–7.30 (5H, m, Ph), 4.11 (1H, ddd, *J* = 9.4, 6.2 and 3.0 Hz, CH(OH)), 3.61 (3H, s, OMe), 2.78 (1H, app. pentet, *J* = 7.0 Hz, CH₃CH), 2.97 (1H, dd, *J* = 16.0 and 3.0 Hz, CH_AH_B), 2.29 (1H, dd, *J* = 16.0 and 9.6 Hz, CH_AH_B), 1.25 (3H, d, *J* = 7.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 173.4, 142.6, 128.5, 128.2, 126.8, 72.3, 51.8, 45.2, 38.8, 17.2; IR (neat): 3657 (O–H), 1727 (C=O), 1438 (C=C), 1254 (C–O), 1162 (C–O) cm^{–1}; HRMS (ES): *m/z* [C₁₂H₁₆NaO₃]⁺ requires 231.0997, found 231.0999.

(+)-(3*S*,4*R*)-4-(*p*-tolyl)pentane-1,3-diol 277b



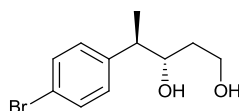
(*E*)-Methyl 4-(*p*-tolyl)pent-3-enoate (**275b**, 0.537 g, 2.63 mmol) was treated according to General Procedure L to afford the title compound as a colourless oil (0.337 g, 66%) in 78% ee, which was determined by General Procedure M; $[\alpha]_D^{26} +6.77$ (c 3.70, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.10-7.19 (4H, m, Ar), 3.77-3.95 (3H, m, CH₂(OH) and CH(OH)), 2.76 (app. pentet, *J* = 7.2 Hz, CH₃CH), 2.34 (3H, s, CH₃Ar), 1.83-1.95 (1H, m, CH(OH)CH_AH_B), 1.62-1.73 (1H, m, CH(OH)CH_AH_B), 1.27 (3H, d, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 139.9, 136.5, 129.5, 127.9, 76.9, 61.9, 46.2, 35.6, 21.0, 17.7; IR (neat): 3373 (O–H), 1052 (C–O) cm^{–1}; HRMS (ES): *m/z* [C₁₂H₁₈NaO₂]⁺ requires 217.1199, found 217.1205.

(+)-(3*S*,4*R*)-4-(4-methoxyphenyl)pentane-1,3-diol 277c



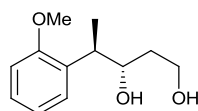
(*E*)-Methyl 4-(4-methoxyphenyl)pent-3-enoate (**275c**, 0.579 g, 2.63 mmol) was treated according to General Procedure L to afford the title compound as a colourless oil (0.426 g, 77%) in 84% ee, which was determined according to General Procedure M; $[\alpha]_D^{26} +8.39$ (c 9.39, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.15-7.21 (2H, m, Ar), 6.85-6.93 (2H, m, Ar), 3.82-3.92 (3H, m, CH₂(OH) and CH(OH)), 3.81 (3H, s, CH₃O), 2.75 (app. pentet, *J* = 7.2 Hz, CH₃CH), 1.82-1.95 (1H, m, CH(OH)CH_AH_B), 1.93 (2H, br. s, OH), 1.58-1.73 (1H, m, CH(OH)CH_AH_B), 1.26 (3H, d, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 158.5, 134.9, 129.0, 114.1, 61.8, 55.3, 45.7, 35.6, 29.5, 17.8; IR (neat): 3391 (O–H), 1244 (C–O), 1025 (C–O) cm^{–1}; HRMS (ES): *m/z* [C₁₂H₁₈NaO₃]⁺ requires 233.1148, found 233.1158.

(+)-(3*S*,4*R*)-4-(4-bromophenyl)pentane-1,3-diol 277d



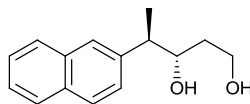
(*E*)-Methyl 4-(4-bromophenyl)pent-3-enoate (**275d**, 0.708 g, 2.63 mmol) was treated according to General Procedure L to afford the title compound as a white solid (0.395 g, 58%) in 85% ee, which was determined according to General Procedure M; $[\alpha]_D^{26} +9.69$ (c 1.76, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.46 (2H, d, *J* = 8.3 Hz, Ar), 7.14 (2H, d, *J* = 8.3 Hz, Ar), 3.77-3.96 (3H, m, CH(OH) and CH₂(OH)), 2.77 (1H, app. pentet, *J* = 7.1 Hz, CH₃CH), 1.96 (2H, br. s, OH), 1.77-1.89 (1H, m, CH_AH_B), 1.54-1.70 (1H, m, CH_AH_B), 1.27 (3H, d, *J* = 7.1 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 142.2, 131.7, 129.9, 120.6, 76.4, 61.8, 46.0, 35.6, 17.6; IR (neat): 3273 (O–H), 1074 (C–Br), 1049 (C–O) cm^{–1}; HRMS (ES): *m/z* [C₁₁H₁₅BrNaO₂]⁺ requires 281.0148, found 281.0160.

(–)-(3*S*,4*R*)-4-(2-methoxyphenyl)pentane-1,3-diol 277e



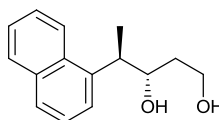
(*E*)-Methyl 4-(2-methoxyphenyl)pent-3-enoate (**275e**, 0.579 g, 2.63 mmol) was treated according to General Procedure L to afford the title compound as a colourless oil (0.249 g, 45%) in 77% ee, which was determined according to General Procedure M; $[\alpha]_D^{26} -4.63$ (c 4.54, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.20-7.27 (2H, m, Ar), 6.85-7.02 (2H, m, Ar), 4.01 (1H, ddd, *J* = 9.9, 7.2 and 2.6 Hz, CH₂CH), 3.78-3.90 (2H, m, CH₂(OH)), 3.85 (3H, s, OCH₃), 3.31 (app. pentet, *J* = 7.1 Hz, CH₃CH), 2.14 (2H, br. s, OH), 1.77-1.89 (1H, m, CH(OH)CH_AH_B), 1.56-1.70 (1H, m, CH(OH)CH_AH_B), 1.26 (3H, d, *J* = 7.1 Hz, CH₃C); ¹³C NMR (75 MHz, CDCl₃) δ 157.3, 131.2, 128.5, 127.7, 121.1, 110.9, 62.2, 55.5, 39.7, 36.0, 29.7, 16.7; IR (neat): 3372 (O–H), 1239 (C–O), 1051 (C–O) cm^{–1}; HRMS (ES): *m/z* [C₁₂H₁₈NaO₃]⁺ requires 233.1148, found 233.1140.

(+)-(3*R*,4*R*)-4-(naphthalen-2-yl)pentane-1,3-diol 277f



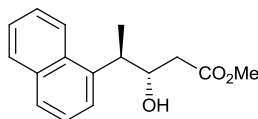
(*E*)-Methyl 4-(naphthalen-2-yl)pent-3-enoate (**275f**, 0.632 g, 2.63 mmol) was treated according to General Procedure L to afford the title compound as a white solid (0.376 g, 62%) in 83% ee, which was determined according to General Procedure M; $[\alpha]_D^{26} +8.56$ (c 0.94, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.78-7.88 (3H, m, Ar), 7.68-7.73 (1H, m, Ar), 7.44-7.52 (2H, m, Ar), 7.41 (1H, dd, *J* = 8.5 and 2.2 Hz, Ar), 4.04 (1H, ddd, *J* = 9.8, 7.6 and 2.6 Hz, CH(OH)), 3.81-3.95 (2H, m, CH₂(OH)), 2.98 (1H, app. pentet, *J* = 7.2 Hz, CH₃CH), 1.88-2.00 (1H, m, CH_AH_B), 1.89 (2H, br. s, OH), 1.64-1.78 (1H, m, CH_AH_B), 1.38 (3H, d, *J* = 7.0 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 140.5, 133.5, 132.6, 128.5, 127.7, 126.9, 126.2, 126.1, 125.7, 77.2, 61.9, 46.8, 35.6, 17.7; IR (neat): 3330 (O–H), 1048 (C–O) cm^{−1}; HRMS (ES): *m/z* [C₁₅H₁₈NaO₂]⁺ requires 253.1199, found 253.1206.

(−)-(3*S*,4*R*)-4-(naphthalen-1-yl)pentane-1,3-diol 277g



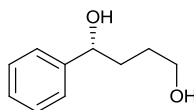
A mixture of (*Z*)- and (*E*)-methyl 4-(naphthalen-1-yl)pent-3-enoate (**275g**, 0.31 g, 1.29 mmol) was treated according to General Procedure L to afford the title compound as a colourless oil (0.122 g, 41%) in 67% ee, which was determined *via* General Procedure M; $[\alpha]_D^{26} -4.83$ (c 3.11, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 8.20 (1H, d, *J* = 7.8 Hz, Ar), 7.86-7.91 (1H, m, Ar), 7.73-7.81 (1H, m, Ar), 7.47-7.59 (4H, m, Ar), 4.21 (1H, ddd, *J* = 9.8, 7.3 and 2.5 Hz, CH(OH)), 3.75-3.95 (3H, m, CH₂OH and CH₃CH), 2.21 (2H, br. s, OH), 1.88-1.99 (1H, m, CH(OH)CH_AH_B), 1.70-1.86 (1H, m, CH(OH)CH_AH_B), 1.40 (3H, d, *J* = 7.0 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 139.5, 134.1, 132.4, 129.0, 127.3, 126.2, 125.7, 125.6, 123.8, 123.3, 76.8, 62.0, 40.2, 35.1, 17.4; IR (neat): 3334 (O–H), 1056 (C–O) cm^{−1}; HRMS (ES): *m/z* [C₁₅H₁₈NaO₂]⁺ requires 253.1199, found 253.1210.

(+)-(3*S*,4*R*)-Methyl 3-hydroxy-4-(naphthalen-1-yl)pentanoate 276g



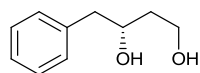
The title compound was also isolated from the above reaction as a colourless oil (0.037 g, 11%); $[\alpha]_D^{26} -7.31$ (c 2.60, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 8.12-8.21 (1H, m, Ar), 7.86-7.92 (1H, m, Ar), 7.74-7.81 (1H, m, Ar), 7.40-7.60 (4H, m, Ar), 4.40-4.49 (1H, m, $\text{CH}(\text{OH})$), 3.93 (1H, app. pentet, $J = 6.5$ Hz, CH_3CH), 3.56 (3H, s, OMe), 2.48-2.54 (2H, m, CH_2), 1.46 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 173.6, 138.9, 134.0, 132.2, 129.1, 127.3, 126.2, 125.6, 125.5, 124.1, 123.2, 71.8, 51.8, 38.7, 37.9, 16.2; IR (neat): 1725 (C=O), 1162 (C–O), 1072 (C–O) cm^{-1} ; HRMS (ES): m/z $[\text{C}_{16}\text{H}_{19}\text{O}_3]^+$ requires 259.1334, found 259.1322.

(+)-(1*R*)-1-phenylbutane-1,4-diol 293³⁷²



(*E*)-Methyl 4-phenylbut-3-enoate (**275h**, 0.463 g, 2.63 mmol) was treated according to General Procedure L to afford the title compound as a colourless solid (0.216 g, 48%) in 70% ee, which was determined *via* General Procedure M; $[\alpha]_D^{26} +18.10$ (c 1.74, CHCl_3); lit. value for epimer: $[\alpha]_D^{25} -28$ (c 1.27, MeOH);³⁷³ ^1H NMR (300 MHz, CDCl_3) δ 7.16-7.37 (5H, m, Ph), 4.66 (1H, t, $J = 6.2$ Hz, $\text{CH}(\text{OH})$), 3.54-3.72 (2H, m, CH_2OH), 3.19 (2H, br. s, OH), 1.79-1.89 (2H, m, $\text{CH}(\text{OH})\text{CH}_2$), 1.59-1.72 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$); ^{13}C NMR (75 MHz, CDCl_3) δ 145.5, 129.1, 128.0, 126.3, 75.1, 63.7, 37.4, 30.1.

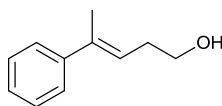
(+)-(3*R*)-4-Phenylbutane-1,3-diol 277h³⁷⁴



The title compound was also isolated from the above reaction as a colourless oil (0.018 g, 4%) in 76% ee, which was determined *via* General Procedure M; $[\alpha]_{\text{D}}^{26} +14.47$ (c 0.36, CHCl_3); lit. value: $[\alpha]_{\text{D}}^{20} +21.0$ (c 0.6, CHCl_3);³⁷⁴ ^1H NMR (300 MHz, CDCl_3) δ 7.12-7.31 (5H, m, Ph), 3.96-4.09 (1H, m, $\text{CH}(\text{OH})$), 3.72-3.88 (2H, m, $\text{CH}_2(\text{OH})$), 2.65-2.81 (2H, m, PhCH_2), 1.65-1.76 (2H, m, $\text{CH}_2\text{CH}_2\text{OH}$), 1.54 (2H, br. s, OH); ^{13}C NMR (75 MHz, CDCl_3) δ 138.1, 129.5, 128.7, 126.6, 73.1, 61.7, 44.4, 37.7.

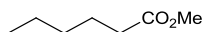
5.12 Investigation into the mechanism of the tandem hydroboration-reduction reaction

(*E*)-4-Phenylpent-3-en-1-ol **287**³⁷⁵



According to a literature procedure,³⁷⁶ (*E*)-methyl 4-phenylpent-3-enoate (**275a**, 1.00 g, 5.26 mmol) was dissolved in a small volume of dry ether, added in one portion to a stirred suspension of LiAlH₄ (0.420 g, 10.52 mmol, 95% purity) in dry ether (40 ml) and the resulting mixture refluxed for 18 hours. After cooling to room temperature, the excess hydride was quenched by cautious addition, down the condenser, of 1.0 M aqueous H₂SO₄ (24 ml) with several additional outlet needles in order to ensure efficient dispersion of the hydrogen gas thus evolved. The aqueous layer was subsequently extracted with ether and the combined organics washed successively with saturated NaHCO₃ solution and water, dried (MgSO₄) and the solvent evaporated under reduced pressure to afford the title compound as a colourless oil in 90% yield; ¹H NMR (300 MHz, CDCl₃) δ 7.22-7.43 (5H, m, Ph), 5.79 (1H, tq, *J* = 7.3 and 1.3 Hz, MeC=CH), 3.76 (2H, t, *J* = 6.5 Hz, CH₂OH), 2.51 (2H, app. q, *J* = 6.9 Hz, CHCH₂), 2.07-2.10 (3H, m, Me); ¹³C NMR (75 MHz, CDCl₃) δ 143.5, 137.8, 128.2, 126.9, 125.7, 123.7, 62.4, 32.4, 16.1.

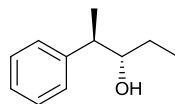
Methyl hexanoate **288**³⁷⁷



Hexanoic anhydride (2.0 ml, 1.86 g, 8.7 mmol) was added to a large excess of methanol (50 ml), followed by 98% H₂SO₄ (0.5 ml). After stirring for three days, an excess of solid NaHCO₃ was added and the methanol removed under reduced pressure. Water and CH₂Cl₂ were added to the residue and the aqueous layer re-extracted with CH₂Cl₂. The combined organic extracts were dried (MgSO₄) and the solvent evaporated under reduced pressure to afford the title compound as a fragrant, volatile, colourless liquid (0.541 g, 48%); ¹H NMR (300 MHz, CDCl₃) δ 3.67 (3H, s, OCH₃), 2.30 (2H, t, *J* = 7.5 Hz, CH₂CO₂CH₃), 1.57-1.69 (2H, m, CH₃(CH₂)₂CH₂), 1.25-1.35 (4H, m, CH₃(CH₂)₂), 0.89 (3H, t, *J* = 6.8 Hz, CH₃CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 174.4, 51.5, 34.1, 31.3, 24.7, 22.3, 13.9.

5.13 Determination of the absolute configuration of diol **277a**

(+)-(2*R*,3*S*)-2-Phenylpentan-3-ol **286**³⁷⁸



According to a literature procedure,³⁷⁹ (+)-(3*S*,4*R*)-4-phenylpentane-1,3-diol (**277a**, 87% ee, 0.106 g, 0.65 mmol) was dissolved in CH₂Cl₂ (2.5 ml) and cooled to 0 °C. To the stirring solution were added Et₃N (0.132 g, 0.18 ml, 1.3 mmol, 2.0 equiv.), DMAP (0.008 g, 0.065 mmol, 0.1 equiv.) and TsCl (0.187 g, 0.98 mmol, 1.5 equiv.). The reaction mixture was stirred overnight at room temperature, quenched by addition of saturated NaHCO₃ solution (10 ml) and extracted with CH₂Cl₂ (3 × 10 ml). The combined organic layers were washed with water (10 ml), dried (MgSO₄) and the solvent removed under reduced pressure to afford a crude tosylate **285** (0.166 g, 84%). Tosylate **285** (0.166 g, 0.5 mmol) was then dissolved in dry THF (2 ml) and added slowly to a stirring suspension of LiAlH₄ (0.019 g, 0.5 mmol, 1.0 equiv.) in dry THF (2 ml).³⁸⁰ After stirring for one hour, the reaction mixture was quenched by addition of a THF-water mixture (1:1 v/v, 10 ml) and diluted with ether (20 ml). The aqueous layer was separated and extracted with ether (3 × 10 ml). The combined organic layers were washed once with water (10 ml), dried (MgSO₄) and evaporated under reduced pressure to afford the title compound as a colourless oil (0.06 g, 56%); $[\alpha]_D^{26} +6.29$ (c 1.59, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.12-7.30 (5H, m, Ph), 3.52 (1H, ddd, *J* = 8.2, 7.1 and 3.5 Hz, CH(OH)), 2.69 (app. pentet, *J* = 7.1 Hz, CH₃CH), 1.49-1.65 (1H, m, CH_AH_B), 1.44 (1H, br. s, OH), 1.24-1.38 (1H, m, CH_AH_B), 1.21 (3H, d, *J* = 7.1 Hz), 0.92 (3H, t, *J* = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 143.6, 128.6, 128.2, 126.7, 77.4, 45.7, 27.3, 18.0, 10.0; IR (neat): 3387 (O–H), 1602 (C=C), 1494 (C=C), 1452 (C=C), cm^{–1}; HRMS (ES): *m/z* [C₁₁H₁₆NaO]⁺ requires 187.1099, found 187.1092.

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